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# HEMORRHAGIC ENCEPHALITIS *

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During the past 15 years we have encountered at autopsy a peculiar involvement of the nervous system. Clinically the patients present a typical picture of encephalitis; pathologically the most striking lesion is a hemorrhagic involvement of the brain. We have called this disease hemorrhagic encephalitis. Because it is so uncommon, a careful review of our cases seems warranted in an attempt to establish certain important clinical and pathological features, and to elicit whatever etiological factors these studies may suggest.

In reviewing the literature on the subject of hemorrhagic encephalitis one is immediately impressed by the great number of reports in which a hemorrhagic condition of the brain followed some infectious, toxic or chemical agent. Such reports have been published by Jacobäus, Schmidt, Abt, Alpers, Winkelman and others. In this study we are concerned, however, with a hemorrhagic disease of the brain which, so far as we can determine, is primary and is not associated with any other pathological condition. Many cases suggesting in their clinical picture encephalitis and showing blood-tinged spinal fluid have been reported as hemorrhagic encephalitis, but most of these patients recovered. This fact renders these reports questionable since the clinical picture is so variable that a postmortem examination is usually necessary to establish the correct diagnosis.

The first cases described which seem to fit the syndrome we are calling hemorrhagic encephalitis were those of Wernicke, published

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in 1881. He reported 3 cases, all of which terminated fatally and which showed at autopsy numerous petechial hemorrhages in the brain substance. In 1885 Strümpell reported 2 cases which clinically resembled encephalitis and which at autopsy showed markedly distended capillaries, hemorrhages in the white matter and some glial proliferation. In neither were the ganglion cells involved. Strümpell considered his cases as examples of a primary, acute hemorrhagic, non-suppurative encephalitis, a term that very aptly describes the malady. Stäussler in 1902 also reported 2 cases of hemorrhagic encephalitis which he considered toxic or infectious in origin, although he was unable to specify the exact cause in either case. His description of the cases, *viz.*, the acute onset in previously healthy individuals and the presence of numerous small petechiae throughout the brain at postmortem, correspond entirely to the condition that we wish to describe. Unfortunately Stäussler did not give a detailed pathological description of the nervous system in his cases.

More recently Grinker and Stone reported a series of cases of non-suppurative encephalitis. Only one of these falls into the category of what we should call hemorrhagic encephalitis. McIntyre reported 20 cases of an unusual encephalopathy, 13 of which had blood in the spinal fluid. Most of these patients recovered, but the few who died did not show any of the brain changes so characteristic of hemorrhagic encephalitis. Therefore, the author was probably dealing with some other condition and not the one under discussion.

## General Features

Our cases of hemorrhagic encephalitis have appeared sporadically during the past 15 years at the rate of 1 to 2 yearly. The condition is probably much more frequent than the number of our cases would lead us to believe, since our acquaintance with it is limited to those cases that are accidentally discovered at autopsy. In only 1 of these was a correct diagnosis made before death. It seems quite likely that numerous fatal cases of hemorrhagic encephalitis occur yearly but are not examined and therefore go undiagnosed. Probably many mild cases also occur. These are treated as one of the more common and better known ailments, and the individuals recover after an illness of varying length. The lack of severe pathological lesions in some of our cases suggests the possibility that many non-fatal lesions

of this hemorrhagic type occur. In no instance have multiple cases of this illness been reported from one family.

A careful review of our histories reveals no significant etiological factors. A few of the patients gave histories of a previous upper respiratory infection, but even these had completely recovered before the onset of the final illness. Diminished resistance due to physical hardship, serious illness, poor living conditions, malnutrition and overwork seems to play no part in the pathogenesis of this disease, since the patients were, with the exception of one child, well nourished and healthy before the onset of illness.

The majority of the cases occurred in patients under the age of 25 years, the youngest was aged 7 months, the oldest 55 years. Younger age groups are evidently predisposed, but that is all one may conclude. The cases were divided about evenly between the sexes.

The lesion in the brain is chiefly hemorrhagic and predominantly in the white matter. The lesions vary widely in number and size. Undoubtedly this variability accounts for the lack of uniformity in the clinical features of the disease. It is this lack of a definite symptomatology that makes the differentiation from other diseases of the central nervous system so difficult. We must recognize the fact that a description of the clinical features of this illness must be comprehensive enough to include many variations. But in spite of these numerous variations, the disease shows a predominance of a certain combination of symptoms and presents a fairly definite entity with its typical onset, course, morbid anatomy and localization in the brain.

## Symptomatology

The prodromata generally make an abrupt appearance in a previously healthy person. These consist chiefly of headache, lassitude, a slight elevation of temperature, and occasionally of nausea and vomiting. These are followed rapidly by graver symptoms. In the extremely acute case the patient soon lapses into unconsciousness, the temperature rises to alarming heights and death occurs within a few hours after the first onset of the illness. Five of our patients were found unconscious. In these no clinical history was available.

In the less acute cases, those where the patient survives a few days to a few weeks, the early prodromal symptoms (headache, lassitude, elevated temperature) are succeeded by a clouding of the sen-

sorium, the patient becomes dazed and confused, and soon lapses into coma. Convulsions of some type are almost always present, but signs of meningeal irritation, such as slight stiffness of the neck, are observed only occasionally.

Pyrexia must be regarded as a nearly constant symptom, since it was present in almost all the cases and usually remained high throughout the course of the illness (Table I). Occasionally a fluctuating type of fever curve is recorded, but this is the exception rather than the rule. The rise in temperature is usually sudden, reaching heights of 106°–108° F. in a few hours after the onset of illness. No very evident relation exists between the degree of the pyrexia and the course of the disease, since some patients with only moderate fever died within a few hours of onset while others with very high temperatures lived for many days.

Convulsions of some kind were recorded as occurring in 12 cases (Table I). These manifested themselves shortly after the onset of illness; some were tonic in character and continuous until death, some were tonic but periodic in occurrence, some epileptiform in nature, others were generalized and clonic in type, while still others were described as "vermicular movements of the upper and lower extremities." As a rule, however, convulsions were generalized and, therefore, of very little localizing significance.

Ocular palsies such as ptosis were not noted, while ocular disturbances were recorded in 4 cases. These varied from very slight changes, such as sluggishness of pupillary reactions in 2 cases, to marked mydriasis in the other 2. In no case was mention made of nystagmus or of the presence of an Argyll Robertson sign. Changes in the eyegrounds were rare. However, a fundus examination was recorded in but half the cases. The changes, when they did occur, consisted merely of a slight blurring of the disk. The involvement of other cranial nerves was rare. In one case (No. 14) there were disturbances in swallowing.

Spasticity of the extremities and reflex disturbances were frequent, although their absence was by no means significant (Table I). With the exception of those extremely acute cases where death took place before careful examination could be made, spasticity of the limbs was a constant finding. The spasticity was either periodic or constant, often persisting throughout the illness. The deep reflexes were described as increased, decreased or unequal. Pathological

reflexes were noted in over one-half the cases in which the reflexes were studied. A striking feature regarding them was their varia-

TABLE I

*Clinical Features of Hemorrhagic Encephalitis*

| Case No. | Temperature | Headache | Convulsions | Altered reflexes | Ocular disorder | Meningeal irritation | Miscellaneous | Found unconscious |
|---|---|---|---|---|---|---|---|---|
| | *F.* | | | | | | | |
| 1 | | | + | | | | | + |
| 2 | | | + | | | | | + |
| 3 | | | | | | | | + |
| 4 | | | | | | | | + |
| 5 | | | | | | | | + |
| 6 | | | + | | | | | |
| 7 | 104° | | − | − | − | − | Nausea, abdominal pain | |
| 8 | 101°–106° | + | − | + | + | + | Sweating | |
| 9 | 91.1° | + | − | − | − | − | | |
| 10 | high | − | + | − | − | − | | |
| 11 | 101°–106.5° | + | + | ? | − | − | Sweating | |
| 12 | 102°–108° | + | − | + | − | − | | |
| 13 | ? | − | + | ? | − | + | | |
| 14 | 104° | + | − | − | − | + | Difficulty in swallowing | |
| 15 | 105° | + | + | + | + | − | Chills | |
| 16 | 100°–107° | + | + | + | + | − | Malaise | |
| 17 | high | ? | + | ? | ? | − | Stupor | |
| 18 | 98°–104.2 | + | + | + | − | − | Stupor | |
| 19 | 106–106.8° | + | + | + | − | − | Vomiting, chills | |
| 20 | 104°–107° | | + | − | + | + | | |

bility from day to day or even from hour to hour. Indeed this rapid change of signs and symptoms was common in our cases.

Certain of the patients gave histories of disturbances of sweat secretion, as well as chills of an indefinite nature, diarrhea and

abdominal pain (Cases 7, 8, 11, 15, 19). Aside from the symptoms referable to the nervous system, the somatic findings were negligible. The heart rate was occasionally increased, but no other significant findings are recorded. The clinical features of our 20 cases of hemorrhagic encephalitis are tabulated in Table I.

To recapitulate, hemorrhagic encephalitis may be characterized as an acute ailment of the central nervous system occurring in previously healthy young individuals and manifesting itself by a sudden onset, headache, an abrupt rise of temperature and a rapid loss of consciousness. Convulsions are common, the extremities are spastic, and the reflexes are frequently abnormal and variable. Death ensues in from a few hours to several days after the onset of illness.

## Laboratory Findings

Blood studies were made in only 8 cases (Table II). The changes in the blood were not pathognomonic. There was usually a moderate leukocytosis, the counts rarely exceeding 25,000 leukocytes per cmm., while in 2 cases the leukocyte count was normal. The white count, like the temperature, gave us no indication as to the prognosis of the disease. In all but 1 case the red blood count was within normal limits. The Wassermann reaction was negative in all the cases.

The cerebrospinal fluid was studied in 12 cases and although not always decisive, often provided the most valuable clue to the clinical diagnosis of the disease. Increased pressure was noted in 5 cases (Table II). The cell count in the spinal fluid varied greatly — from none to a large number. Five cases showed no pleocytosis but in the others the cells varied from 10, 35 and 50 cells per cmm. to as high as 560 cells per cmm. in 1 case (Case 20). In many of the fluids polymorphonuclear leukocytes were numerous, often constituting as many as half the cells.

The spinal fluid was generally clear but in 4 cases it was slightly blood-tinged (Table II). It is this latter finding that should make one suspect this ailment. Whenever a bloody spinal fluid is obtained, together with the above clinical picture, hemorrhagic encephalitis must be considered in the differential diagnosis. In only an occasional case, however, do the cerebral hemorrhages approach close enough to the surface of the brain or ventricles to give a blood-tinged fluid.

TABLE II

*Laboratory Findings in Hemorrhagic Encephalitis*

| Case No. | White blood count | Red blood count | Spinal fluid | |
|---|---|---|---|---|
| | | | pressure | cells |
| 3 | *per cmm.* | *per cmm.* | | *per cmm.* Bloody |
| 6 | | | Clear Normal pressure | 3 cells |
| 7 | | | Clear Normal pressure | 5 cells |
| 8 | 9,500 (83% P.M.N.) | 5,136,000 | Clear Increased pressure | 10 cells |
| 9 | 16,300 (82% P.M.N.) | | | |
| 10 | 8,000 | 4,150,000 | Clear Increased pressure | 35 cells |
| 11 | | | | Bloody |
| 12 | | | Clear Normal pressure | 2 cells |
| 15 | 17,000 | | Clear Increased pressure | 50 cells |
| 16 | 14,000 (91% P.M.N.) | 4,600,000 | Clear Normal pressure | Bloody |
| 18 | 11,600 (85% P.M.N.) | | Increased pressure | Bloody |
| 19 | 21,100 (81% P.M.N.) | | Clear Normal pressure | 10 cells |
| 20 | 25,000 (71% P.M.N.) | 2,160,000 | Increased pressure | 560 cells |

The spinal fluid Wassermann reaction was invariably negative. The urine examinations did not reveal any pathological changes.

## CLINICAL DIFFERENTIAL DIAGNOSIS

Although most of our experience has been with the very acute and rapidly fatal form of the disease, it is likely that a considerable number of cases may take a milder form and recover. Numerous transitory cerebral disturbances may be due to this masked form of the disease. Unfortunately, the absence of a blood-tinged spinal fluid

precludes a clinical diagnosis of hemorrhagic encephalitis, even in the extremely severe cases. However, we feel certain that since we meet about 2 cases yearly in our autopsy service, the condition must be more prevalent than this number would seem to indicate and that many cases must escape our attention either because of recovery or misdiagnosis.

It is because of the difficulty of diagnosis that we are unable to make even a tentative statement regarding the prognosis or the sequelae of this disease. A statement of the mortality would be justified only if we knew some method of detecting the milder cases.

The differential diagnosis in hemorrhagic encephalitis must be discussed from two points of view, namely the clinical and the pathological. The latter will be treated in detail in a later paragraph. The scope of this paper does not permit a complete discussion of each of the numerous clinical conditions with which this disease might be confused. We must content ourselves here with merely listing them, together with some of their most complete references.

Clinically the disease that resembles our cases most closely is the lethargic encephalitis of von Economo. Especially is this true of the somnolent form which bears a striking similarity to our cases. Among the numerous other conditions which resemble hemorrhagic encephalitis clinically are: the bulbar type of poliomyelitis; the encephalitis following smallpox and rabies vaccination (Gordon and Rhea, Wilson and Ford, Flexner, Denson, Scott, Hekman, Huber); the encephalitides following the infectious diseases, measles (Lowenburg and Schaller, Skoog, Guthrie, Smith, Box, Fox, Fairbanks, Beach, Jenkins, Bruce, Ford, Horwitt, Walthard), scarlet fever (Boenheim, Neurath, Schilder), typhus (Jarisch, Feldmann, Grodzki, Morawetz), whooping cough (Askin and Zimmerman, Bertoye, Mikulowski, Boenheim), and dysentery (Lenhartz, Buttenwieser); the encephalitides resulting from the various metallic poisonings such as lead (Hassin, Kato, Lewin and Treu, Waterfield, Barron and Habein), and arsenic (Fischer, Hahn, Globus and Ginsburg); the acute form of disseminated sclerosis; the cerebral involvement following botulism (Wilbur and Ophüls, Meyer, Cox, Smith), and alcoholism (Gamper, Ohkuma, Neubürger, Bender and Schilder); cerebral syphilis; brain tumors; meningitides, chiefly tuberculous; influenza (Mouriquand, Bernheim and Boucomont, Eiwin and Wurman, Elmer and Boylan); certain cases of subacute bacterial

endocarditis; and finally cases of spontaneous subarachnoid hemorrhage. The last two conditions deserve particular mention because they may show, besides their confusing clinical history, a blood-tinged spinal fluid, which is the one essential feature in the clinical diagnosis of hemorrhagic encephalitis. In some cases of subacute bacterial endocarditis small emboli lodge in the brain, producing areas of infarction. If these cerebral infarcts are situated close to the surface of the brain or the ventricles, a bloody spinal fluid might be present. We have studied one such case that clinically presented a typical picture of hemorrhagic encephalitis, including the bloody spinal fluid. At autopsy the correct diagnosis was readily apparent. Spontaneous subarachnoid hemorrhage occurs most frequently in young people, and if the bleeding is slow, the numerous clinical findings, together with the bloody spinal fluid, make a diagnosis very difficult. Forbus has studied this subject and has shown that in young people the bleeding is most often due to rupture of an aneurysm of a superficial cerebral artery.

## Pathological Alterations

The lesions found at postmortem in hemorrhagic encephalitis constitute the essential characteristic feature of this disease. Unfortunately, though the lesions are fairly characteristic, they are not pathognomonic. Numerous other conditions (which will be discussed later) may produce a somewhat similar anatomical picture. However, with a good history at hand one should be able, in the presence of the pathological features to be described below, to arrive at a correct diagnosis of this disease. Strümpell, in 1885, was the first to describe the fundamental features of the cerebral involvement in hemorrhagic encephalitis. He considered his cases characteristic enough to constitute a pathological entity, which he described as a "primary, acute, hemorrhagic, non-suppurative encephalitis."

The dura mater shows no change, except for occasional congestion of its vessels. The leptomeninges are also normal, except in a few cases in which they show moderate hyperemia and diffuse edema. There is no thickening or purulent involvement of these membranes. The cerebrospinal fluid pressure may be increased, but the convolutions of the brain do not appear flattened. In 2 of our cases there was

a diffuse thin layer of blood beneath the arachnoid. These extravasations were quite marked, covering a large surface of the cortex and producing a bloody spinal fluid. Careful examination of the brain surfaces revealed no definite bleeding point. Two other cases (Nos. 18 and 20) showed on the surface of the cortex large areas of discoloration and softening, which on section proved to be large hemorrhagic areas that had destroyed the brain tissue and extended from the white substance into the cortex. In only 1 of these cases had the erythrocytes actually broken into the subarachnoid space to produce a blood-tinged spinal fluid (No. 18).

Generally, therefore, (16 of our 20 cases) the external gross appearance of the brain is normal, although occasionally the hemorrhagic process is obvious, even from the external examination.

Coronal sections through the brain reveal a uniform and striking gross picture. Scattered irregularly through the brain, but without localization to a particular region, are numerous sharply circumscribed hemorrhages of variable size and number. These are characteristically located in the white substance, with only an occasional petechia appearing in the cortex (Fig. 1). In many cases the hemorrhages are very small, few in number and either scattered diffusely throughout the tissue or collected in tiny groups in certain regions of the brain, particularly around the ventricles. In other cases these tiny hemorrhages are extremely numerous, completely filling the tissue and producing a speckled appearance in the gross section. These hemorrhages are often so small that it is difficult to determine grossly whether they are true bleeding points or merely dilated vessels. Upon microscopic examination under moderate magnification the true nature of the tiny extravasations can readily be perceived.

In some sections larger, widely scattered, irregular areas are encountered which have the appearance of confluent punctate hemorrhages. These are often surrounded by numerous petechiae of smaller size. The larger hemorrhages are found only in sections where the smaller ones are numerous and are closely packed together, suggesting that these larger hemorrhages are formed by the fusion of the smaller ones. The brain tissue does not appear softened or altered about any of these medium sized hemorrhages.

In an occasional case very large hemorrhages are found (2 of our 20 cases) (Fig. 2). These may be so extensive that they destroy large areas of brain tissue. They not infrequently extend through the

cortex into the subarachnoid space or into the ventricles. These are the solid masses of blood that are visible as discolored areas upon external examination of the brain. Around these massive hemorrhages are seen many minute to moderate sized effusions of blood. Again one gains the impression that the larger extravasations are formed by the fusion of numerous smaller ones. The brain tissue surrounding these large hemorrhages is softened and necrotic.

The large vessels at the base of the brain and their branches are normal. There is no evidence of any sclerosis, thrombosis, or embolism. In none of the cases was there found an aneurysm of these vessels.

The great variation in degree of the hemorrhagic cerebral involvement in this condition can be illustrated by briefly contrasting the gross appearance of the brains in 2 of our cases (Nos. 15 and 20). In the first of these the hemorrhages were almost entirely small and discrete (Fig. 1), while in the second they were massive and accompanied by a large amount of injury to the brain tissue (Fig. 2).

Case 15 was that of a 55 year old female who died after an illness of but a few days duration. At autopsy the meninges appeared normal. Aside from slight distention of the small vessels, no sign of any pathological disturbance was apparent from the external examination of the brain. Serial sections, however, revealed a very extensive hemorrhagic involvement (Fig. 1). Throughout the brain substance there were numerous, small, petechial hemorrhages which, although variable in size and number, always remained comparatively small. These hemorrhages were chiefly disseminated throughout the white substance. There were a few small groups in the subcortical region of the parietal lobes. These at no time fused to form large hemorrhages. Only a few scattered points of bleeding were found in the brain stem and none at all in the cerebellum. The brain tissue did not seem softened, even in the region of the most numerous hemorrhages. The ventricles were clear and their walls contained no accumulation of red cells. The findings in this case illustrate the small, uniform, punctate type of lesion so commonly seen in hemorrhagic encephalitis of the rapidly fatal type. These hemorrhages are occasionally so small (No. 19) that grossly one is unable to determine whether they are true extravasations of blood or merely dilated vessels.

In contrast to this case, No. 20 exemplifies those with massive

irregular hemorrhages and with a marked destruction of brain tissue (Fig. 2). This patient, a child, died 2 weeks after the onset of illness. On external examination of the brain, the pathological involvement was immediately apparent. On the inferior surface of the left frontal lobe and on the lateral surfaces of the left parietal and temporal lobes of the brain there appeared a purplish discoloration and a marked softening of the cortex. The right half of the cerebrum, the pons, the medulla and the cerebellum seemed normal externally. Sections revealed a marked involvement of the left half of the brain and a much milder process on the right.

Sections through the left cerebral hemisphere revealed large hemorrhages containing fresh and old blood, and a marked destruction and softening of the brain tissue. The hemorrhages varied in size from pin-point extravasations to confluent areas measuring 7 to 9 cm. in diameter and containing masses of old clotted blood. A large area of involvement was present in the anterior portion of the left frontal lobe where the necrotic brain substance extended almost to the cortex. In the left parietal and temporal regions the hemorrhage involved large areas of the white substance and extended through the cortex to the surface of the brain, but did not break through into the subarachnoid space. The left occipital lobe contained only an occasional small hemorrhage. In the upper part of this region there was a single hemorrhage measuring 1 cm. in each dimension. The ventricles were free from blood, although numerous petechiae were scattered throughout their walls. The basal nuclei were strikingly free from involvement.

The right half of the brain contained numerous, small petechial hemorrhages scattered through the white substance, the internal capsule, and the anterior extremities of the caudate and of the lenticular nuclei. This latter region appeared somewhat softened. The right lateral ventricle was free from blood, although the tissue surrounding its anterior horn was hemorrhagic and necrotic. This area was the only one in the right half of the brain in which the hemorrhages assumed a notable size, surpassing in magnitude the lesions described in the previous case.

The lesions described in the left half of this brain present a striking contrast to those in No. 15. Our series of cases presented all gradations between the extremes described above, as well as all possible degrees of dissemination and types of localization of the lesions.

## Microscopic Alterations

### *Normal Brain*

To appreciate fully the microscopic changes appearing in the central nervous system in hemorrhagic encephalitis, it is necessary to have a thorough understanding of the normal histology of the cerebral vessels, as well as the normal variations that may be encountered in a routine study of apparently normal brains within any single age group. In order to study the normal brain we selected from our coroner's service thirty apparently normal brains from individuals under 35 years of age, all of whom died from some extracerebral condition such as gun-shot wounds of the abdomen or various other abdominal conditions. Brains of younger people were used in order to eliminate the problem of normal age changes, and to facilitate a comparison with our cases of hemorrhagic encephalitis which usually occurred in younger individuals.

The arteries that supply the brain are quite different from similar sized arteries in other parts of the body. The average small cerebral artery is characterized by a well developed elastica interna, and a media composed of a large amount of collagenous tissue with a few elastic fibrils and muscle fibers. The adventitial coat is scanty or entirely absent.

The internal elastic lamina is the most conspicuous part of the cerebral vessel and is both relatively and absolutely thicker than in similar sized vessels elsewhere. Often fine elastic fibrils can be observed extending outward from the elastica interna and branching through the medial layer.

The media consists of concentrically arranged, anastomosing collagenous fibers, among which are found some smooth muscle tissue and a few elastic strands. With the azocarmine stain it is apparent that even in young individuals the collagenous tissue is relatively much more abundant in the cerebral arteries than in arteries of corresponding size elsewhere.

The adventitia is often entirely absent in the small cerebral arteries. When it is present it consists of a few strands of collagenous fibers which partially or completely surround the medial layer.

The arteries of the white substance of the brain differ somewhat from those of the cortex in that they contain even less muscle in their media.

A more complete description of the cerebral vessels will appear in a separate publication.

In a survey of a series of normal brains there were found about the vessels a few changes which occur often enough to indicate that they are apparently not of pathological significance. Most of the capillaries and tiny arterioles are empty and collapsed, or at most contain but few erythrocytes. The larger arterioles and the small arteries are often filled with red cells. In some normal brains, however, many of the capillaries are distended, and in still others all of the cerebral vessels from the smallest to the largest are full of erythrocytes. Occasionally a small vessel is observed about which a very thin collar of erythrocytes can be seen. This perivascular hemorrhage, if severe, is a definite lesion, but it may be detected occasionally about vessels in normal brains. These extravasations are always very small and consist of only a few cells which partially surround the vessel. A few arteries are observed which present a slight increase of mononuclear cells in and about their outer walls. From these observations it becomes apparent that a moderate capillary dilatation, an occasional perivascular hemorrhage, or slight mononuclear infiltration, must be considered in the range of normal variation.

Our routine microscopic studies of the nervous system included sections taken from numerous cortical areas, the basal ganglia, the midbrain, the cerebellum and the medulla oblongata. These were stained in one or more of the following ways: hematoxylin-eosin, Weigert's myelin sheath stain, iron hematoxylin-Van Gieson, Nissl's method, Bielschowsky's stain, Sudan III stain for fat, Cajal's gold sublimate stain, and del Río-Hortega's silver carbonate method. The last two methods proved the most successful in our hands in demonstrating the detailed structure of the astrocytes and microglia. In both of these methods the fresh tissue was fixed in Cajal's formalin-ammonium-bromide solution; the tissue that had already been fixed in formalin was subjected to bromuration. This latter process was suggested by Globus. It consists in placing formalin-fixed tissue in distilled water to which has been added one drop of strong ammonium hydroxide for each cc. of water. The tissue is left in this solution overnight, then washed and placed in a 10 per cent hydrobromic acid solution for 1 to 3 hours. Sections are then ready for impregnation with either gold or silver.

*Appearance of Brain in Hemorrhagic Encephalitis*

The most characteristic feature of the microscopic appearance of the brain in hemorrhagic encephalitis is the presence of numerous hemorrhages that vary in magnitude from extensive extravasations which destroy much brain tissue to tiny perivascular bleedings. All degrees of variation can be found between these two extremes. Usually the hemorrhages are scattered irregularly throughout the white substance of the cerebrum, occasionally some are grouped together in certain regions, while the rest of the tissue contains only dilated capillaries or a few perivascular erythrocytes. The hemorrhages, unless very extensive, are strictly limited to the white substance. When they are large they may tear through the cortex and reach the surface of the brain (Fig. 3). These massive hemorrhages are usually surrounded by petechiae of variable size. It is often possible to reconstruct the successive stages in the fusion of these petechiae to form the larger hemorrhagic areas. In many cases what appears grossly to be solid masses of extravasated blood is readily recognized microscopically to consist of a conglomeration of numerous small hemorrhages.

Most of the small hemorrhages assume a perivascular arrangement (Fig. 4). The earliest stage in their formation consists of a few erythrocytes scattered about the tiny vessels. When the larger arteries are involved the red cells at first fill the perivascular lymph space, tearing the glial fibers away from the vessel wall. As the hemorrhages increase in size, they break through the ring of glial tissue into the surrounding tissue, causing various degrees of injury to the brain and the interruption of some of the nerve fibers in the vicinity. Sections taken shortly after this tissue injury has occurred show little or no reaction of the cerebral elements, but after a few days extensive alterations are visible. These changes will be discussed in a later paragraph.

*Ball of Solid Hemorrhages:* Bleeding from the larger vessels always results in solid accumulations of red cells termed "ball hemorrhages." These, either singly or fused, are by far the most frequent type of hemorrhage observed in the brain (Fig. 5). Although they often are so numerous that they replace large areas of brain tissue, they have a tendency to remain discrete. They usually have at their center a ruptured vessel (Fig. 4). In many, the vessel is not visible,

although the rounded uniform arrangement of the hemorrhage certainly suggests a vascular origin. The vascular injury that permits these solid hemorrhages to be formed can be demonstrated by carefully studying the walls of the involved vessels. In the early cases little or no change can be detected in spite of a most careful study. Evidently sufficient time has not elapsed for the morphological changes to occur. One of the earliest changes apparent in the vessels is a loss of the normal staining reactions in certain portions, suggesting an early degeneration. This is followed by a thinning out of certain areas of the elastic lamina with a resultant defect of the wall. In the smaller vessels the collagenous layer of the wall is too thin to provide a sufficient support in those regions where the elastica has degenerated, and soon one may detect a bulging of the weakened wall and a streaming of red cells through into the surrounding tissue. The larger arteries have a thicker supporting collagenous membrane and a few muscle fibers which prevent bleeding even after the elastica interna has thinned out and ruptured. However, in some of these arteries, after the elastica has degenerated, the collagenous fibers of the media also become frayed and torn in various areas. The erythrocytes then follow the tears in the wall and eventually break through to the outside. Many vessels present a swelling and hyaline degeneration of the elements of their walls. There is a loss of differentiation into the normal layers and the walls become homogeneous and rupture.

Still another change is frequently observed, especially about the smaller vessels. This consists in endothelial proliferation which may be moderate, replacing the vessel wall, or so extensive as to reach tumor-like dimensions. No hemorrhages are observed about these vessels, suggesting that the endothelial proliferation has probably strengthened the walls sufficiently to prevent rupture and hemorrhage.

*Ring Hemorrhages:* Another type of hemorrhage which often occurs is the so-called ring hemorrhage. This presents a clear uninvolved center surrounded by a dense ring of erythrocytes (Figs. 6, 7). It is caused by the rupture of numerous tiny capillaries which surround the larger vessels. They, therefore, take the form of a partial or complete ring, depending upon the degree of capillary disruption. When the capillary damage is very severe the red blood cells infiltrate into the clear center of the ring, producing the appearance of a

solid hemorrhage, with the exception that the hemorrhage in these cases is usually less dense in the center than in the periphery. Often the clear centers of these ring bleedings consist of degenerated brain tissue infiltrated with numerous scavenger cells. The damage to the brain tissue surrounding these hemorrhages is similar to that in the solid type and, as in those, depends upon the size of the extravasation.

*Diffuse Hemorrhages:* The cerebral hemorrhages are not necessarily limited to the region of the blood vessels but often appear as diffuse extravasations (Fig. 8). When only a few erythrocytes are found scattered through the nervous tissue there seems to be no definite injury to the immediate structures. As these diffuse hemorrhages become more extensive the damage to the brain tissue increases. In the small hemorrhages the red cells merely push the cerebral fibers apart without causing them to rupture, but the increase in the number of erythrocytes results finally in a rupture of many of the fibers, followed by demyelinization and infiltration of fat granule cells. This latter picture can be very readily demonstrated with a modified silver stain (Fig. 9).

*Perivascular Demyelinization:* When death occurs in hemorrhagic encephalitis within the first 24 hours of the disease, hemorrhages alone are detectable in the brain substance. Undoubtedly some damage has occurred, but insufficient time has elapsed for evidence of that injury to become visible microscopically. Many patients survive the first few days, and in these it is easy to observe the characteristic alterations in the brain tissue which may not only accompany the hemorrhages, but may also occur independently of them. The latter changes usually occur about the blood vessels, producing a perivascular demyelinization (Fig. 10). The perivascular alterations are at first very slight, consisting of myelin destruction with a beginning infiltration of scavenger cells (Fig. 11). In the more advanced stages the perivascular demyelinization is extensive, and the infiltration of scavenger cells filled with fatty débris is marked. A slight proliferative reaction of the neuroglia situated near the periphery of the destroyed area may now be detected. The end result of this destructive process is a complete demyelinization around the vessel (Fig. 10). The destroyed area ultimately contains only a few scavenger cells, but there is a great increase in glial fibers laid down by the proliferating astrocytes. There are no hemorrhages about

these vessels. These areas of non-hemorrhagic perivascular demyelinization strongly suggest the possibility that in this disease some neurotoxin is disseminated by means of the cerebral vessels and produces either vessel injury and hemorrhage, or no vessel injury but perivascular tissue damage, depending upon its localization.

The cytological changes that occur both in the non-hemorrhagic degenerated areas and in the tissue surrounding large hemorrhages are similar and will, therefore, be described together. The chief cellular elements involved in cerebral injury are the microcytes and the astrocytes. Special stains are essential for a detailed study of these elements. These stains have been listed in a previous paragraph.

*Microglial Changes:* The normal microglial cells were first studied in detail in 1921 by del Río-Hortega who worked out their morphological and structural details, their transformation into rod cells and fat granule cells, their motility and their phagocytic functions. This author firmly believed that these cells are mesodermal in origin. This view is widely accepted (Penfield, Jiménez de Asúa, Belloni, Ramirez Corria, Russell and others). Numerous names have been applied to this cell, such as Nissl's Stäbchenzellen, ameboid wandering cells, granulo-adipose cells, Gitterzellen, compound granular cells, scavenger cells and fat granule cells. The last two terms will be used interchangeably in this discussion.

The microglial cells invade areas of cerebral damage and remove the destroyed tissue. In order to discharge their functions these cells develop marked migratory and phagocytic properties. Shortly after a brain injury occurs, regardless of the nature of the injurious agent, these cells draw in their processes and move toward the injured area. After reaching the site of injury they may increase in size and number (Fig. 12). Some investigators still doubt their migratory ability, but sufficient evidence is available to establish their migratory and phagocytic powers. The tendency of these fat-laden scavenger cells to accumulate about the blood vessels and even to invade their lumens speaks strongly for their migratory faculty.

The normal resting microglial cells can usually be identified with the routine nuclear stains, since their nuclei are the smallest in the nervous framework and are variable in shape, being round, oval or triangular. They contain a large number of deeply staining chromatin granules and have a distinct nuclear membrane. Their cytoplasm is not visible with ordinary stains. Special staining reveals a scanty

cytoplasm which is prolonged into numerous wavy and branched processes that gradually thin out and terminate some distance from the cell body. Normal microglial cells may be unipolar, bipolar, or multipolar; the latter are the most frequent (Fig. 12).

In the early destructive changes in hemorrhagic encephalitis the increase in the number of microglial cells is slight. Most of these cells are elongated to form the so called "rod cells." The transitions between these rod forms and the normal microglia can readily be demonstrated in a study of the invading cells. As del Río-Hortega and Penfield have pointed out, there is a gradual retraction of the cell processes, resulting in the formation of cells with elongated nuclei and two broad bands of perinuclear cytoplasm. These cells have a typical rod shape. Only an occasional cell is seen that has developed into the rounded fat granule form. When fat stains are applied in this early stage only a few of the altered forms are found to contain fat granules, since the rod cells do not possess marked phagocytic ability. If the patient succumbs early in the disease, this is as far as the morphological changes have advanced.

The older degenerated lesions are filled with typical scavenger cells. As one passes from the normal tissue into the injured areas the complete metamorphosis of the microglia into rod cells and finally into fat granule cells is readily observed. The latter cells are globular in form, have no cytoplasmic processes and vary widely in size and shape (Fig. 11). They are usually filled with fat droplets. They are very abundant in the regions of severe degeneration and represent an advanced stage in the process of the phagocytosis and removal of destroyed tissue and extravasated red blood cells. A fat stain applied to material at this period shows all stages in the process of phagocytosis. Some cells contain only a few fat granules; others are completely filled. The scavenger cells vary in size from small cells with a central nucleus and a few fine fat droplets to large, irregular bodies in which the nucleus becomes eccentric or is entirely invisible because of the large accumulations of fat. Many cells reach tremendous dimensions. These are often multinucleated. A perivascular arrangement of these fat-filled cells was not observed in any of the sections. A moderate amount of fat may be observed lying free in the demyelinated areas.

In the periphery of the larger hemorrhages the fat granule cells ingest not only fat but also red cells and parts of red cells. Pecul-

iarly, hemorrhages do not stimulate the changes in the microglia in the absence of brain injury. Granule cells were never found around the smaller hemorrhages. Their faculty for ingesting red cells seems to be subordinate to the removal of the fatty débris.

Some scavenger cells undergo degeneration, and present pyknosis of the nuclei and a cytoplasmic disintegration. These cells are infrequent, but quite characteristic when present.

*Changes in the Astrocytes:* When the microglial cells have accomplished their phagocytic function and have begun to decrease in number, the astrocytes begin to undergo various proliferative changes. The normal resting astrocyte possesses an irregularly oval, pale staining nucleus which contains a few scattered chromatin granules. The cell body is large and radiating from it are numerous branching processes of variable length and thickness. These cells proliferate only in the final stages of the tissue destruction. The neuroglial proliferation is accompanied by a swelling both of the nucleus and of the cell body. The cytoplasm becomes finely granular and the nucleus becomes larger and more irregular, often polymorphous. Accompanying this hypertrophy there is an increase in size and number of the cell fibers, producing a zone of fairly intense gliosis. The astrocytes in the immediate vicinity of the larger hemorrhages undergo degenerative changes due to pressure of the hemorrhagic extravasations. They swell, the cytoplasm becomes coarsely granular and the processes become fragmented and scattered. Their nuclei become smaller and pyknotic. In many of these cells both the nucleus and the processes disappear, leaving only a granular degenerating cell body. The large degenerating astrocytes are scattered among the numerous fat granule cells that have invaded the dead tissue. Occasionally a cell of this type contains a few fine fat droplets, but they are never observed engorged with fat as are the scavenger cells. Apparently normal astrocytes within an area of degeneration never contain fat droplets. The fact that these cells contain such small amounts of fat, in spite of their presence in the center of the necrotic demyelinated area, speaks against their phagocytic ability.

*Nerve Cell Changes:* Consistent specific changes in the ganglion cells have not been observed in our cases of hemorrhagic encephalitis. This favors the view that alterations in these cells are due to the destructive action of the large hemorrhages which occasionally rup-

ture into the cortex. Scattered through these regions in which the hemorrhage has involved the gray substance are found isolated ganglion cells showing various degrees of degeneration — fragmentation of their processes, shrinkage of the cell body and eccentricity or complete absence of the nucleus. Other cells are large and swollen with a granular vacuolated cytoplasm and a complete absence of the cell processes. All stages in the degeneration of the nerve cells can be observed from slight swelling to complete homogeneity, disintegration and dissolution. With the Nissl stain these cells show partial to complete chromatolysis. There is no neuronophagy. The injured ganglion cells are not replaced by glial cells. The nerve cell changes do not occur simultaneously over large areas of cortical substance, but are found in only a few ganglion cells here and there within the dead brain tissue surrounding the larger hemorrhages.

A search for specific inclusions in an attempt to relate this condition to the virus diseases has been fruitless to date.

Occasionally a blood vessel is observed with slight perivascular infiltration of mononuclears. A few widely scattered polymorphonuclear leukocytes are occasionally observed in the area of degeneration. One of the brains contained a slight increase in polymorphonuclears, but the lesions were predominantly hemorrhagic and necrotic.

No attempt will be made to describe the microscopic findings in the nervous system of each individual case. However, the essential pathological features of each case in which sufficient material was available for study are summarized in Table III.

The internal organs show no characteristic findings. The lack of pulmonary involvement is quite striking, particularly in view of the fact that some of the patients complained of upper respiratory symptoms sometime before the onset of illness. When lung complications are present they are mostly terminal in nature. The other internal organs similarly show no pathological features.

### Pathological Differential Diagnosis

The pathological picture just described is, in itself, hardly diagnostic of hemorrhagic encephalitis since a similar one may occur in numerous other conditions. This is not surprising, since it is recognized that the central nervous system may react in a similar manner to a large variety of irritants. It is, therefore, essential to obtain a detailed history and physical examination and to perform a careful

autopsy in order to elucidate the etiological factors responsible for the hemorrhagic picture. Cerebral hemorrhages have been reported in such diverse conditions as: the encephalitides following measles, scarlet fever, dysentery, typhus; poisoning with arsenic, methyl

TABLE III

*Microscopic Alterations in the Brain in Cases of Hemorrhagic Encephalitis*

| Case No. | Nerve cell injury | | Brain tissue injury | Microcyte infiltration | Perivascular demyelinization | Petechial hemorrhages | Large hemorrhages | Diffuse hemorrhages | Localized hemorrhages | Tissue injured around hemorrhage | Perivascular hemorrhage | Alterations in vessel wall | Thrombosis of vessels | Infiltration of mononuclears |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chromatolysis | Other changes | | | | | | | | | | | | |
| 1 | − | − | ± | − | − | + | + | + | − | + | + | ± | − | ± |
| 2 | − | − | − | − | − | + | ± | + | − | ± | + | − | − | − |
| 3 | − | − | − | − | − | + | − | + | − | − | + | − | − | − |
| 4 | − | − | − | − | − | + | − | − | + | − | + | ± | − | − |
| 5 | − | − | − | − | − | + | − | + | − | − | + | ± | − | ± |
| 7 | − | − | − | − | − | + | − | + | − | − | + | + | − | − |
| 9 | − | − | + | ± | ± | + | ± | + | − | − | + | + | − | + |
| 10 | − | − | + | + | ± | + | − | + | − | − | + | + | − | + |
| 11 | ± | ± | − | − | − | + | − | + | − | − | + | + | − | ± |
| 12 | − | − | − | − | ± | + | − | + | − | − | + | + | − | − |
| 13 | − | − | − | − | − | + | − | − | + | − | + | ± | − | ± |
| 14 | − | − | − | − | − | + | − | + | − | − | + | − | − | − |
| 15 | + | + | + | + | + | + | + | + | − | + | + | + | − | − |
| 16 | − | − | − | + | + | + | − | + | + | + | + | + | − | − |
| 17 | − | − | − | − | ± | + | − | + | − | − | + | ± | ± | ± |
| 18 | ± | ± | + | + | ± | + | + | + | − | + | + | + | − | − |
| 20 | + | + | + | + | + | + | + | + | − | + | + | + | − | − |

chloride, phosphorus and alcohol; trauma to the head without skull fracture; fat embolism after fracture of bones; and hemorrhagic or venous infarction of the brain. We have had the opportunity to study the cerebral lesions in many of these conditions, and a discussion of the findings in these, in order to facilitate a comparison between them and hemorrhagic encephalitis, seems warranted.

### *Arsenic Poisoning*

The cerebral lesions of arsenic encephalitis are often hemorrhagic. It is for this reason that it has been called "hemorrhagic encephalitis" or "purpura hemorrhagica" by investigators such as Pritzi, Pines and Prigonikow, Almkvist, and Scott and Moore. The cerebral hemorrhages are so common in individuals dying of arsenic poisoning that some investigators have been led to believe that all sudden unexplained deaths in which hemorrhages are found in the brain are due to poisoning with this substance. This contention seems to gain strength from the observation that a faintly positive Reinsch, Marsh, or Gutzeit test for arsenic is obtained from the brain tissue of an occasional one of these cases. However, arsenic is so commonly used in industry and is so widely distributed in nature, that it is not surprising that small quantities should constantly enter the human body. The amount of arsenic normally present in adults would naturally vary greatly, depending upon the character of the individual's food, drink, medication or environment. As Myers has shown, this more or less normal ingestion of small amounts of arsenic renders a positive chemical test alone, as a criterion for arsenical death, inconclusive.

Since the introduction of arsenicals in the treatment of syphilis, cerebral accidents known to be caused by arsenic have increased. In 1933 Globus and Ginsburg reviewed the literature on this subject. They found 74 cases with complete autopsy findings, although numerous incomplete cases have been reported (Almkvist, Hahn, Nonne, Pritzi, Mingazzini). A review of 1 case in our service will help clarify the clinical picture and the pathological features of this condition.

CASE 1. A. H., a 21 year old white female, was admitted to the hospital unconscious. She had recently been exposed to syphilis and 11 days before admission she had received 0.6 gm. of neosalvarsan intravenously, followed 6 days later by a similar injection. Two days after this second treatment she suddenly developed a severe headache, lost her appetite and became lethargic. The following day she was more listless and developed generalized convulsions. The family physician who was called obtained an incomplete history. Finding a marked rigidity of the neck he made a tentative diagnosis of meningitis and ordered the patient to the hospital. Upon admission to the hospital she was comatose, her neck was rigid and her blood pressure 130/80. The chest and abdomen appeared normal. Reflexes were normal, but the neurological examination was otherwise unsatisfactory because of the patient's condition. A confluent macular eruption covered her arms and shoulders.

*Laboratory Examination:* The urine was normal. The white blood count was 13,000 with 68 per cent polymorphonuclears and 31 per cent lymphocytes. The blood sugar was 0.14 per cent, urea nitrogen 30.1 mg. per 100 cc. of blood, creatinin 2 mg. per 100 cc. of blood, and the icterus index was 13. The spinal fluid was normal in appearance and under normal pressure.

The patient's temperature was 102° F. on admission. It rose rapidly to 106° F., where it remained until the time of death, which occurred on the second day of the hospital stay.

*Autopsy:* External examination of the body revealed mottling of the lateral surface of the right shoulder, the right arm and the left hip, with very tiny, closely-set petechial hemorrhages. Nothing else of note was observed externally. The pleural and pericardial membranes were normal. The heart showed a few, scattered, subepicardial petechiae but was otherwise negative. The lungs were somewhat heavier than normal and showed marked posterior hypostasis and a slight terminal pneumonia. A few tiny hemorrhages were scattered through the bladder wall. The remaining organs, with the exception of the brain, appeared normal.

The scalp, calvarium and meninges were all normal. Coronal sections through the brain revealed numerous small hemorrhages. Bilaterally in the white substance at the lateral inferior margin of the putamen there were softened areas measuring 2.5 by 1.5 cm., surrounded by numerous hemorrhages. In the anterior medial portions of both temporal lobes in the region of the uncus and amygdaloid nuclei, there were other slightly softened areas surrounded by densely packed petechiae. Many hemorrhages were seen on the inferior surface of the corpus callosum, on the superior and lateral walls of the lateral ventricles, and in the posterior portions of the brain.

*Microscopic Examination:* The most characteristic feature is the presence of numerous hemorrhages scattered throughout the white substance (Fig. 13). Extravasations are chiefly around the capillaries and precapillaries and, therefore, are mostly of the ring type. They vary in size, extending occasionally only into the perivascular spaces, but more often involving the surrounding tissue. A few lymphocytes and polymorphonuclears are found within the hemorrhages. In places the extravasations are so numerous and diffuse that they fuse to form massive hemorrhages. Numerous small hemorrhages are also observed in the cerebral cortex. Many of the vessels are injured, showing endothelial swelling as well as hyalini-

zation of the vessel walls. Numerous vessel walls are infiltrated with polymorphonuclear leukocytes and lymphocytes. The vessel changes occur with or without perivascular hemorrhage. There are frequently found in the vessels hyaline or cellular thrombi that completely fill their lumens (Fig. 13). There is no destruction of brain tissue, either about the non-hemorrhagic injured vessels or at the periphery of the hemorrhages. No reaction is observed on the part of the neuroglia or of the microglia. The large nerve cells are intact. The characteristic findings of syphilis, namely perivascular and diffuse lymphocytic infiltration, as well as endarteritis, are altogether lacking.

*Comment:* The findings in this case correspond with those reported in the literature. Thrombosis of vessels appears to be a very common occurrence (Pritzi, Wechselmann, Scott and Moore, von Marschalkó, and others). The question of the localization of the hemorrhages in the white substance of the brain is somewhat unsettled. In our case, extravasations were also observed in the cerebral cortex. This is in agreement with the observations of Almkvist and Post, although other investigators have been able to detect them only in the white substance. Nonne and Mingazzini have reported hemorrhagic lesions involving both the gray and white matter of the cord.

How does this pathological picture compare with that of hemorrhagic encephalitis? Although the hemorrhages may be very similar, there are some pathological features that facilitate their differentiation. The presence of hemorrhages in the cord and cerebral cortex, of lymphocytic and polymorphonuclear infiltrations, of numerous thrombosed vessels, and of petechiae in other organs are all foreign to true hemorrhagic encephalitis and should make one suspect some other condition. However, the microscopic variations are usually insufficient to warrant the differentiation, and one must rely upon the history, together with supplementary chemical tests, for the diagnosis of arsphenamine poisoning.

In none of our 20 cases of hemorrhagic encephalitis was the history in the least suggestive of arsenic poisoning. However, because of the resemblance of the cerebral lesions to those in arsenic poisoning, and also because some individuals have claimed that this chemical is the causative agent in cases similar to ours, we tested three brains from our series of true hemorrhagic encephalitis, together with four nor-

mal controls, for the presence of arsenic. One hundred gm. of tissue from each brain was used and tested by the Marsh method. One brain of true hemorrhagic encephalitis showed a faint trace of arsenic, while the rest were all negative. Of the controls, three showed similar traces of the arsenic. All the chemicals used in the test, as well as the formalin, proved negative for arsenic. This, we believe, is adequate proof that the etiological factor in our cases is not arsenic.

Several other substances, such as methyl chloride, phosphorus and alcohol have been reported as producing cerebral hemorrhages, but our personal experience has not included such cases. These are not disturbing clinically, however, since a careful history usually permits a correct diagnosis.

### *Methyl Chloride Poisoning*

Methyl chloride poisoning was first described by Gerbis in 1914. Since then 72 cases with 11 deaths have been reported. In man, cerebral hemorrhages are very uncommon, although they are quite characteristic of the lesions produced in the brains of guinea pigs exposed experimentally to the gas.

### *Phosphorus Poisoning*

Spielmeyer was one of the first to describe cerebral hemorrhages as a result of phosphorus poisoning. Such cases are infrequent. The chemical usually does not produce cerebral symptoms. Wertham, in reviewing the literature on this subject, has pointed out that by far the most frequent cerebral lesion is a destruction of the nerve cells. Vascular injury with bleeding is rare.

### *Alcohol Poisoning*

Cerebral hemorrhages are occasionally found in patients dying of alcoholism, an observation first made by Wernicke. His original paper cited 3 cases, only 1 of which followed alcoholism. Since this publication Wernicke's work has been confirmed by Bender and Schilder, Marchiafava and Kant. It appears that these hemorrhages are by no means constant. When they do occur there is a tendency for them to localize in the cortex.

### *Infectious Encephalitis*

Cerebral symptoms following severe infections are frequent. Since most of the cases recover, only a few rather incomplete autopsy reports are available for study (Mouriquand, Bernheim and Boucomont, Eiwin and Wurman, Parnell and Dudley). Schmidt, as early as 1905, reported a series of cases of cerebral hemorrhages in septic diphtheria and pneumonia, while Grinker and Stone published 5 cases in which cerebral symptoms were apparently due to some toxin in the nasopharynx. These workers believed that any severe upper respiratory infection might be responsible for such cerebral involvement. Numerous isolated reports of cerebral hemorrhage have been recorded following specific infectious diseases such as measles, dysentery, typhus and scarlet fever (Musser and Hauser, Buttenwieser, Herzog). These cerebral hemorrhagic manifestations following infections are uncommon and almost always the history, together with other postmortem findings, is sufficient to point to the correct diagnosis. Two cases of postinfectious cerebral hemorrhage have come under our observation, one following scarlet fever and the other pneumonia. A clinical and pathological description of these cases is given to enable one to contrast them with our cases of true hemorrhagic encephalitis.

CASE 1. A white male, aged 39 years, was admitted to the hospital in a very critical condition. He had been ill for several days. At the time of admission a complete pneumonic involvement of both lungs was found. The patient died a few days later in a septic state.

*Autopsy:* The lungs were heavy and almost completely consolidated. The other internal organs were essentially normal, with the exception of slight cloudy swelling of the liver and kidneys. The external examination of the brain was negative. Coronal sections revealed numerous discrete petechiae scattered throughout the entire white substance (Fig. 15). There was no tendency to localize in any particular region. The cortex contained but few extravasations. No tissue necrosis was apparent. The ventricles were clear.

*Microscopic Examination:* There is marked distention of the cerebral arteries. Numerous tiny vessels are dilated and filled with blood. Many ring hemorrhages are scattered through the white substance. These are uniform in size and shape. Accumulations of erythrocytes about the larger vessels, as well as diffuse hemorrhages

independent of vessels, are uncommon. Very little change is detected in the vessel walls, although an occasional vessel is thrombosed. No tissue injury is observed nor is there any cellular reaction visible. The nerve cells are somewhat shrunken but their processes are still intact. This case, because of its clinical features and because of the pathological findings in the lungs, offers but little difficulty in the way of diagnosis.

CASE 2. A white female, aged 32 years, was suddenly taken ill with a sore throat, fever, chills and restlessness. The following day she developed a generalized bright red rash which a private physician diagnosed as scarlet fever. During the next few days she became slightly irrational, restless, noisy and uncontrollable. She was, therefore, sent to the hospital. Past infectious diseases included measles, mumps and whooping cough.

On physical examination, the patient was found to have a temperature of 105.8° F. and a pulse of 132. The blood pressure was not recorded. She was very restless and irrational, and mumbled indistinctly. Her face was flushed, the skin was hot and dry, and there was a generalized erythema of the skin over the trunk and extremities, on which was superimposed a fine, discrete, pin-point eruption about the hair follicles. The pupils were equal and reacted to light. The mouth showed an erythematous mucous membrane; the soft palate and uvula were swollen and red. The remainder of the physical examination was negative.

On admission the patient's temperature was so high and the delirium so marked that it was deemed advisable to give her scarlet fever antitoxin. The following day the rash had almost entirely faded. However, she developed generalized rhonchi throughout both lungs, and soon became cyanotic. Respirations became irregular and she died on the following day.

The blood count showed 83 per cent hemoglobin, 4,610,000 erythrocytes, 16,700 leukocytes, with a differential count of 90 per cent polymorphonuclears and 10 per cent mononuclears.

*Autopsy:* The external examination revealed no rash but there was a slight, fine desquamation about the cheeks. Aside from the lungs, the internal organs showed nothing of note. The lungs were heavy and almost completely consolidated. On section they were found to be dark red in color and full of pus.

External examination of the head showed the scalp and calvarium to be normal. Coronal sections of the brain revealed definite petechial hemorrhages scattered throughout the posterior portion of the corpus callosum on each side. These hemorrhages were almost 1 mm. in diameter. A few similar petechiae were found scattered throughout the white substance of the brain, particularly in the left occipital lobe. The middle ears and mastoids were normal.

*Microscopic Examination:* Sections of the brain reveal numerous small areas of hemorrhage, all of which show marked hemolysis. No

definite red cell outlines are visible in any of these hemorrhagic areas. The relation of these petechiae to the small vessels cannot be determined because of the hemolysis in the areas. The cerebral cortex and the meninges are normal.

*Comment:* Cerebral hemorrhages following scarlet fever have been reported by various investigators. Southard and Sims in 1904 studied a case both clinically and pathologically. Their patient, who was 5 years old, developed cerebral symptoms 7 weeks after the onset of the acute exanthem. At autopsy a large number of hemorrhagic areas which extended down through the cortex into the white substance of both parietal lobes were found. Microscopically numerous large petechiae were visible in the gray substance of the parietal lobes. Surrounding these hemorrhages there were numerous phagocytes which were invading the hemorrhagic areas and taking up the polymorphonuclears, red blood cells and fat. The nerve cells showed various degenerative changes. Signs of frank suppuration were also found in these necrotic areas. Toomey, Dembo and McConnell in 1923 described a similar case. In their case, however, the brain appeared normal externally, although both ventricles were filled with blood. On section there were numerous hemorrhages into the basal nuclei. Microscopically many of the blood vessels were thrombosed and there was a destruction of the vessel wall resulting in the perivascular extravasations.

### *Purpura Hemorrhagica*

A primary or secondary purpura may produce cerebral hemorrhages of sufficient severity to cause death. These purpuras almost always show, aside from the cerebral lesions, signs of bleeding elsewhere in the body. Such widely distributed hemorrhages, together with the other findings of purpura, should enable one to arrive at the correct diagnosis of the underlying condition. Intracranial hemorrhages in purpura have been reported by Duplay, Jousset, Duplaix, and Alpers and Duane. All of their cases presented other characteristic clinical features of purpura, aside from the terminal cerebral bleeding. Recently we have had occasion to study one such case.

CASE 1. The patient, aged 36 years, had been treated for renal calculi, pyelonephritis and cystitis. He had had multiple stones removed from the left ureter and from the bladder. A few days before admission to the hospital he was suddenly seized with pain over the left kidney. This pain radiated down the left

side to the scrotum. It was accompanied by chills, fever and a little urgency and burning on urination. On admission to the hospital examination revealed a blood pressure of 90/60 and a temperature of 99° F. A cystoscopic examination showed a slight cystitis with no return of indigocarmine from either ureter in 15 minutes. The urine contained much pus, erythrocytes and epithelial cells. Roentgen-ray studies revealed a right pyelonephritis and a left ureteral calculus.

Shortly after admission the patient developed severe epistaxis, for which he was given hemostatic serum. Nevertheless, he not only continued to bleed from the nose but began to bleed also from the mouth, bladder, rectum and finally into the subcutaneous tissues. A spinal tap at this time revealed a blood-tinged fluid. The patient's respirations gradually became irregular. Shortly before his death the hemorrhage from the mucous surfaces became very profuse.

Laboratory studies showed a red blood count of 3,560,000, hemoglobin 70 per cent, non-protein nitrogen 163 mg. per 100 cc. of blood, creatinin 3.2 mg. per 100 cc. of blood, coagulation time of 7 minutes, bleeding time 12 minutes, and platelet count 184,000. His temperature varied from 99° to 100.2° F.

*Autopsy:* The body was covered with numerous petechiae situated beneath the skin and varying in diameter from 1 mm. to 1 cm. There were small ecchymotic areas in the sclerae of both eyes. Petechial and ecchymotic areas were also observed over the serous surface of the heart and in the kidneys, liver and bladder. Aside from these hemorrhages there was a bilateral pyelonephritis, with renal calculi filling the entire pelvis of the left kidney.

The surface of the brain was covered with a thin film of blood. There was a clot measuring 2.5 cm. in diameter in the anterior fossa under the right frontal lobe. A softened area was observed in the right frontal lobe anterior to the lenticular nucleus. Scattered through this region were numerous old and new hemorrhages. There was an extensive hemorrhage 6 by 4 by 4 cm. in the left occipital lobe. This lesion extended into the lateral ventricle medially, and to the external surface of the brain laterally. There was extensive destruction of brain tissue throughout this massive hemorrhage. In the dentate nucleus of the right cerebellum there was a hemorrhage measuring 2.5 by 2.3 by 2 cm.

*Microscopic Examination:* This reveals extensive hemorrhages and destruction of the cerebral tissue (Fig. 14). Massive diffuse extravasations of red cells have infiltrated the cerebral tissue, causing much destruction both in the white and gray substance (Fig. 14). These hemorrhages do not involve the entire brain but are localized in the various regions listed, causing much local damage. They appear to be fresh and there is no reaction on the part of the supporting elements of the brain. No fat granule cells or rod cells can be found

in the damaged areas. Throughout the tissue not involved in this massive bleeding there are occasional small, discrete, perivascular hemorrhages. These vary in size from just a few erythrocytes to a fairly large extravasation that not only fills the perivascular space but also extends into the surrounding tissue. The red cells in these areas of hemorrhage are very peculiar in appearance, most of them being fragmented and elongated. No alterations of any kind can be detected in the vessel walls. No thrombi are observed in the vessels. The nerve cells appear uninjured.

### *Traumatic Encephalitis*

The marked increase in automobile accidents has elevated the problem of trauma to the head to one of major importance. Among these traumatic lesions there are many that are diagnosed cerebral concussion or contusion in which no fracture of the skull has occurred, and from which the patient may die or from which he may recover with residual complaints of an indefinite nature. Many investigators have studied these brains and have observed definite organic lesions in many of them (Bennett and Hunt, Osnato and Giliberti, Cassasa, Jefferson, Trotter, Head). Osnato and Giliberti in a careful examination of a series of cases which terminated fatally found numerous diffuse hemorrhages scattered throughout the brain tissue. There was no reaction on the part of the cellular elements. They suggested the term "traumatic encephalitis" for these lesions. Similar changes have been reported by Cassasa.

We have had the opportunity to study such a case of cerebral trauma following an accident, in which no skull fracture had occurred and in which the gross sections of the brain showed a resemblance to the true hemorrhagic encephalitis (Fig. 16).

CASE 1. A male, aged 45 years, was injured in an automobile accident and died after 4 days of unconsciousness. At autopsy numerous abrasions were observed over the face and scalp. There were fractures of numerous ribs on both sides but no skull fracture. A slight amount of terminal pneumonia was present bilaterally, although most of the lung tissue was fairly normal. The other internal organs appeared normal.

On removal of the brain a considerable amount of subdural hemorrhage was found in the right posterior fossa. Careful sectioning of the brain revealed numerous discrete hemorrhages scattered through the entire brain substance but more prominent in the white

matter (Fig. 16). Close scrutiny of the sections showed small traumatized areas distributed through the brain. These contained softened hemorrhagic brain tissue and were constantly situated near the surface. These lesions were suggestive of a traumatic origin.

Microscopically, numerous perivascular hemorrhages of both the ring and the solid type are seen throughout the brain tissue. These hemorrhages are most numerous in the white substance, although many are also observed in the cortex. The cortical hemorrhages are often of a diffuse nature, extending to the surface of the brain. There is no tissue injury about the perivascular hemorrhages and no reaction on the part of the cerebral elements. In the traumatized regions there is extensive tissue destruction together with some hemorrhage, the former constituting the most prominent part of the picture. The injury involves not only the entire cortical substance but often extends into the subcortical regions.

It seems from the above protocol that in some cases of cerebral concussion or contusion, the pathological findings resemble somewhat those of hemorrhagic encephalitis, but the history of a preexisting head injury, the external signs of severe bruising of the body, and a careful examination of the brain for traumatized areas usually permits a correct diagnosis.

### *Fat Embolism*

Fat embolism of the brain may follow fracture of various long bones. It produces cerebral petechiae which grossly might be confused with hemorrhagic encephalitis. A fat stain, however, readily demonstrates the tiny fat emboli filling the vessels about which the hemorrhage has occurred.

### *Hemorrhagic or Venous Infarct*

Although hemorrhagic or venous infarcts are comparatively rare, they should be mentioned briefly in this discussion, since upon cursory examination they might be confused with those cases of true hemorrhagic encephalitis in which extensive extravasations have occurred. Venous infarction was described as early as 1913 by Oeller, who called the condition "hemorrhagic encephalitis." He considered it an inflammatory thrombosis of the smaller or larger veins of the brain with resulting rupture of the capillaries because of increased

arterial pressure. Recently we have had occasion to study such a case in a 27 year old female who was admitted to the hospital because of a pelvic inflammatory condition. After a short stay, she suddenly developed hemiplegia of the left side of the body. She gradually lapsed into coma and died. At autopsy a small circumscribed abscess containing dark brown necrotic material was found near the hilum of the right lung. A small fresh infarct was present in the upper pole of the spleen. The left tube and ovary were fused to form a large mass, which on section contained a small amount of dark, thin, purulent material. Gross examination of the scalp and calvarium was negative. On removing the dura a large thrombosed vein was seen extending along the left hemisphere from the Sylvian fissure, posteriorly and downward to the occipital pole of the brain. The brain tissue immediately beneath this vessel was hemorrhagic and necrotic. Coronal sections of the brain revealed numerous softened hemorrhagic areas involving the entire cortex and subcortical tissue along the course of this large thrombosed vein. There were no hemorrhages found elsewhere. Microscopic examination shows numerous thrombosed pial veins with many petechial hemorrhages in their immediate neighborhood; inflammatory changes are already evident within many of these degenerating regions.

The presence of thrombosed veins and the absence of hemorrhages and necrosis, except about these injured veins, is sufficient to distinguish this condition from true hemorrhagic encephalitis.

## Etiology of Encephalitis

The etiology of many types of encephalitis is still undetermined in spite of the extensive experimental work that has been done. The scope of the present paper does not warrant a complete discussion of the very numerous and widely scattered reports on the etiology of encephalitis. It can be stated at the outset, however, that with few exceptions no conclusive evidence has been presented to show that encephalitis in man is due to a virus infection, a cultivatable bacterium, or a toxicosis, although these are the three prevailing views. Most investigators, at the present time, tend to favor a virus infection as the etiological factor in many types of human encephalitis, although there has developed a marked difference of opinion as to how this agent really acts. The main trends of thought are in two

directions. One group of investigators believes that the cerebral involvement in encephalitis is due to a specific, neurotropic, invisible, but as yet undiscovered virus infection (Stern, von Economo, McKinley, and Flexner in epidemic encephalitis; Bijl and Frenkel, Gildemeister, Turnbull and McIntosh, Flexner, and Scott in post-vaccination encephalitis; Pette and Wohlwill in measles encephalitis; Gordon in mumps encephalitis). The other school maintains that some environmental factor or infectious disease breaks down the natural resistance of the individual and thus predisposes him to an infection by some non-specific and often detectable virus. Levaditi, Doerr and Schnabel, Berger, Doerr and Zdansky, Gay and Holden advocate a herpes virus in epidemic encephalitis; Loewe and Strauss, immobile "globuli" in epidemic encephalitis; Gay and Holden, a herpes virus in measles encephalitis; Strümpell, the poliomyelitis virus in epidemic encephalitis.

During the course of this study fresh brain tissue was obtained from a case of hemorrhagic encephalitis (Case 20). In coöperation with Dr. C. Buggs from the department of bacteriology, a virus was isolated from this tissue and was carried through twelve serial transmissions in rabbits by means of intracerebral inoculation. The infectious brain tissue does not affect mice or guinea pigs.

The micropathological alterations observed in the rabbit brains resemble in many details those changes found in the human cases of hemorrhagic encephalitis. So far a detailed examination for inclusions has not been instituted.

A detailed description of the experimental studies in rabbits will be given in a separate publication.

Twenty cases of hemorrhagic encephalitis have been studied at postmortem. A brief report of each of these follows.

## Case Reports

Case 1. Male, aged 33 years, apparently well until 10 A.M. on the day of his death when he was found unconscious at work. He was taken to the hospital where he had repeated attacks of generalized convulsions. He died 5 hours after the onset of the illness without regaining consciousness.

*Autopsy:* Negative with the exception of the brain. The left lateral ventricle contained a slight amount of blood. Numerous petechial hemorrhages could be seen in the region of this ventricle and in the pons. A few larger diffuse hemorrhages were also present.

*Microscopic Examination:* Petechiae are found only in those areas in which hemorrhages are visible on gross examination. These hemorrhages are mainly perivascular. Around some of the larger hemorrhages there is a slight amount of tissue destruction but no fat granule cells are seen. An occasional small vessel in the pons is surrounded by a few mononuclear cells.

CASE 2. Female, aged 25 years, found unconscious and taken to the hospital. She showed no evidence of paralysis, although she was quite spastic and had attacks of epileptiform convulsions. Death occurred shortly after admission to the hospital.

*Autopsy:* Negative with the exception of the brain. Small hemorrhages were visible throughout the brain tissue. Numerous small hemorrhages were scattered through the white substance of the brain and a few were localized in the basal nuclei.

*Microscopic Examination:* These hemorrhages are both perivascular and disseminated. No cellular infiltration is visible.

CASE 3. Male, aged 41 years, was found unconscious at work and died about 4 hours later. He had been working regularly up to the onset of his attack. The spinal fluid was bloody.

*Autopsy:* Negative except for the brain. The entire under-surface of the brain was covered by a fine film of blood. Careful examination of the surface of the brain revealed no contusions or ruptured vessels. On sections of the brain numerous petechiae were found in the pons and medulla and around the ventricles.

*Microscopic Examination:* The hemorrhages are small and localized around the blood vessels. In sections through the pons particularly, almost every small vessel is surrounded by a wide zone of red cells. No cellular infiltration is observed within the brain tissue.

CASE 4. Female, aged 36 years, was found one morning dead in bed. She had been in apparent good health.

*Autopsy:* Negative except for the brain, sections of which revealed many small hemorrhages scattered throughout the white matter of the cerebral hemispheres.

*Microscopic Examination:* The hemorrhages are mostly perivascular. No cellular infiltration is visible.

CASE 5. Male, aged 40 years, died suddenly while sitting in a barber's chair.

*Autopsy:* Negative except for the brain. (Careful examination of the coronaries revealed no lesions.) Grossly the scalp, skull, meninges and brain showed no conspicuous lesions.

*Microscopic Examination:* Multiple small hemorrhages are scattered diffusely through the cerebral hemispheres. Occasionally the hemorrhages are arranged perivascularly. No marked cellular infiltrations are visible.

CASE 6. Female, aged 14 months, had always been in good health. She was playing in the house when she was suddenly seized with generalized convulsions occurring at approximately 3 minute intervals. She was taken to the hospital where she died 3 hours after the onset of the illness.

*Autopsy:* Negative, except for the brain which was congested and on section revealed numerous pin-point hemorrhages scattered chiefly throughout the occipital lobes, the temporal lobes and the basal nuclei.

*Microscopic Examination:* These hemorrhages are both diffuse and perivascular in distribution. No cellular infiltration is apparent. The spinal cord is negative both grossly and microscopically.

CASE 7. Male, aged 25 years, developed a cold about 1 month before his present illness from which he apparently had recovered. He was well until 5 days before his death when he suddenly developed nausea, vomiting and dizziness. These symptoms persisted, and 2 days later he became irrational and stuporous. This stupor deepened into a coma which lasted until his death. The blood and spinal fluid Wassermann were negative.

*Autopsy:* Aside from the presence of a horseshoe kidney, the findings were negative with the exception of the brain. The external surface of the brain was normal, but on section numerous small pinpoint hemorrhages were detected throughout the white matter of the cerebral hemispheres.

*Microscopic Examination:* The small hemorrhages are mostly perivascular, consisting of rather dense collars of blood cells surrounding the smaller vessels and extending into the surrounding brain tissue. The vessels are also filled with erythrocytes. No cellular infiltration is visible. Cultures of the brain and of the heart muscle are negative.

CASE 8. Male, aged 44 years. Illness started 2 weeks before death with a severe headache and general malaise. The headaches increased in severity and he gradually became listless, irrational, and finally stuporous. He perspired profusely. A physical examination was performed shortly before the onset of stupor.

His face was flushed and the facial expression was dull. He responded slowly when spoken to, giving fairly intelligent replies; however, frequently during the examination, he dropped into a semicomatose condition from which he could easily be aroused. The pupils were irregular, the right one did not react to light, while the left one reacted but slightly. There was a coarse tremor of the tongue and the neck was slightly rigid. His reflexes varied, being normal on one day and hyperactive on the next. The Babinski sign also varied from day to day. The red blood count was 5,136,000; white blood count 9500; polymorphonuclears 83 per cent, lymphocytes 17 per cent. The blood and spinal fluid Wassermann reactions were negative. The spinal fluid was under increased pressure, and showed 10 cells per cmm.

His condition gradually grew worse. The temperature rose from 101 to 106° F., the coma deepened and he died 2 weeks after the onset of the illness.

*Autopsy:* Negative except for the brain. Grossly there was a reddish tinge to the brain tissue in the regions of the frontal lobe, the temporal lobe and the basal nuclei. No hemorrhages were visible.

*Microscopic Examination:* All the vessels of the brain are markedly distended with blood. Surrounding the vessels, chiefly in the frontal and temporal lobes, are numerous perivascular hemorrhages. Occasionally areas of hemorrhage apart from vessels are seen. These are most numerous in the frontal and temporal lobes. No cellular infiltration is visible.

CASE 9. Male, aged 18 years, always well and active. He suddenly began to complain of occipital headaches and dizziness. Shortly afterwards he developed a marked weakness of the left forearm and hand and of the right leg. There was twitching of the involved muscles. The patient became very restless. His reflexes remained normal. The temperature gradually rose, and he died 2 days after the onset of illness.

*Autopsy:* Negative except for the brain which contained numerous small hemorrhagic areas.

*Microscopic Examination:* Many small perivascular and diffuse hemorrhages are found throughout the white matter. Small areas of degeneration are visible in the white matter, especially about the periphery of the hemorrhages, but only slight cellular reaction has as yet occurred. Occasional vessels are surrounded by mononuclear cells.

CASE 10. Male, aged 35 years. The first indication of illness was a marked personality change followed shortly by weakness and drowsiness. He became irrational, his muscles became spastic, and he developed generalized convulsions. The red blood cell count was 4,150,000, hemoglobin 80 per cent, the white blood count 8000. The urine was negative. A spinal tap showed a clear fluid under in-

creased pressure. There were 35 cells per cmm. The Wassermann tests were negative. The temperature rose rapidly and he died 4 days after the onset of illness.

*Autopsy:* Negative except for the brain. On section the brain showed many small hemorrhages in the white matter.

*Microscopic Examination:* The hemorrhages are both perivascular and diffuse. Some of the larger ones are surrounded by damaged brain tissue. Numerous scavenger cells have already invaded these demyelinated regions. A few of the vessels are surrounded by cuffs of mononuclears.

CASE 11. Male, aged 14 years. Illness started suddenly with headache and vomiting. A few hours after the onset of this illness there occurred generalized convulsions and the patient lapsed into unconsciousness. His temperature at this time was normal. On the following day it had risen to 101° F. and the convulsions persisted. There was never any neck rigidity, the Kernig sign remained negative. A spinal tap showed a slightly bloody fluid. The temperature gradually rose to 106.5° F. and the patient died 3 days after the onset of illness.

*Autopsy:* Negative except for the brain. The vessels over the surface of the brain were distended. There was a small amount of free blood in the subarachnoid space around the base of the brain. Sections of the brain revealed numerous pin-point hemorrhages scattered throughout the white and gray substance. Many of the bleeding points were near the surface.

*Microscopic Examination:* The small hemorrhages are mostly perivascular. There is an occasional petechia in the cortex. The basal nuclei are moderately involved. Some of the vessels are surrounded by a few mononuclear cells. Many of the large nerve cells of the cerebral cortex and of the basal ganglia show chromatolysis and pyknosis of their nuclei.

CASE 12. Female, aged 36 years. Illness first started with the complaint of headache. When her husband returned from work that evening, he found her unconscious but not paralyzed. She was immediately removed to the hospital.

The physical examination revealed very few findings. The pupils were equal. The right upper extremity was spastic, while the left upper and right lower extremities were flaccid. The blood pressure was 110/80. The urine examination was negative. The spinal and blood Wassermann tests were negative. During her stay in the hospital she never regained consciousness. Her pulse varied between 130 and 150 and her temperature between 102°–108° F. She died 3½ days after the onset of illness.

*Autopsy:* Negative except for the brain, which showed many petechial hemorrhages throughout the white matter. These hemorrhages were also very numerous in the basal nuclei.

*Microscopic Examination:* The hemorrhages are both free and perivascular in type. No cellular infiltration or nerve cell degeneration is visible.

CASE 13. Male, aged 3 years. Had always been very robust, and before the onset of his present illness showed no signs of any infection. While eating bread one day, he complained of feeling ill. His eyes became fixed, his arms and legs showed a marked spasticity and his head became stiff and retracted. Drowsiness gradually set in and he died about an hour after the onset of illness. No one else in the family eating the same bread became ill.

*Autopsy:* Negative except for the brain. The vessels in the brain were prominent. On section it was difficult to determine whether we were dealing with dilated vessels or true hemorrhages. Most of the lesions seemed to be in the temporal and occipital lobes of the brain, involving the gray matter as well as the white.

*Microscopic Examination:* Most of the small vessels of the brain are distended with blood. True hemorrhages of the perivascular type are found only in the temporal and occipital regions involving both the gray and white matter. A few small mononuclear cells are found around some of the dilated vessels.

CASE 14. Male, aged 5 years, had apparently always been in good health. He was suddenly taken ill with headache, and malaise. A physician was called, who found the boy moderately ill. His temperature was 101° F., pulse 120, and there were no signs of an upper respiratory infection. A few hours after the onset of illness, the child's neck became stiff and he experienced slight difficulty in swallowing. His temperature gradually rose to 104° and he died 9 hours after the onset of the illness.

*Autopsy:* Negative except for the head. Numerous small hemorrhages were scattered throughout the base of the brain, the pons, and the upper part of the medulla.

*Microscopic Examination:* The hemorrhages are both diffuse and perivascular. No polymorphonuclear cells are discovered. There is no meningitis.

CASE 15. Female, aged 55 years. She had been well until the onset of the present illness. While working in her garden she experienced a severe headache. A physician was called who found her temperature to be 102° F. The next day she was restless and had a severe convulsion which consisted of spasmatic contractions of the muscles of all her limbs. She soon lapsed into unconsciousness and

was admitted to the hospital in this condition. At that time her pupils reacted sluggishly to light, but the ophthalmoscopic examination revealed normal findings. The blood pressure was 108/64. The urine was normal. A spinal puncture showed the fluid under increased pressure, with 50 cells per cmm. Her temperature gradually rose to 105° F., the coma deepened, she had occasional tonic convulsions and died 6 days after the onset of illness.

*Autopsy:* The gross appearance of this brain is described in detail elsewhere in this paper.

*Microscopic Examination:* Most of the hemorrhages are perivascular, although some larger diffuse ones can be observed extending up into the cortex. There is marked tissue destruction around the larger hemorrhages. There is perivascular demyelinization around vessels not surrounded by erythrocytes. Reactions on the part of the microglia and neuroglia are readily visible. There is no lymphocytic infiltration into the tissue.

CASE 16. Female, aged 11 years, had always been well until the present illness which started with a severe headache. She became feverish and complained of extreme aching in her bones, back and head. These complaints continued for 2 days, when she suddenly became unconscious and had what her mother described as a series of generalized convulsions which lasted for 1 hour. From that time on she did not regain consciousness. She had athetoid movements of the arms and hands. Her legs were alternately spastic and flaccid. On admission to the hospital the child was in a deep coma. The lower extremities were spastic while the upper were athetotic. The knee jerks were exaggerated; there was an unsustained ankle clonus; and the Babinskis were bilaterally positive. A spinal puncture showed no increased pressure; there was a pleocytosis. The urine was negative. The red blood count was 4,600,000, hemoglobin 83 per cent, white blood count 14,000, with 91 per cent polymorphonuclears and 9 per cent lymphocytes. The Wassermann test was negative.

The child's signs and symptoms varied greatly during hospitalization. The reflexes at one time would be exaggerated and the extremities spastic, while a few hours later the reflexes would be decreased or absent and the extremities flaccid. Her temperature rose to 107° F., the pulse increased to 140, the coma continued, and the child expired 7 days after the onset of illness.

*Autopsy:* The lungs showed a slight edema and a beginning pneumonia. Otherwise the findings were negative except for the brain, which on section revealed numerous hemorrhages throughout the white substance, being most marked in the occipital regions.

*Microscopic Examination:* The hemorrhages are both diffuse and perivascular in arrangement. Numerous vessels show marked perivascular demyelinization with the characteristic reactions on the part of the scavenger and glial cells. No involvement of the cortex is observed.

CASE 17. Female, aged 2½ years. She had always been well. Her illness first manifested itself with a slight restlessness and a moderate elevation of temperature. A few hours later she developed generalized convulsions which continued until the time of death, 12 hours after the onset of illness.

*Autopsy:* Negative except for the brain. There was an engorgement of the pial vessels. Sections of the brain suggested small hemorrhages throughout the white matter.

*Microscopic Examination:* There is a marked distention of the cerebral vessels, many of which are surrounded by a collar of erythrocytes which in some cases extend beyond the perivascular spaces and into the brain substance. A few small vessels are surrounded by mononuclear cells. Only an occasional polymorphonuclear is detected in and around the vessels. There is no change in the ganglion cells. The cord is negative.

CASE 18. Male, aged 20 years. During the past few days his family noticed that he had been lying down quite frequently and sleeping more than usual. However, since he had always been healthy no attention was paid to this lack of spirit and exaggerated fatigue. He continued to work hard, until one morning he suddenly developed generalized convulsions. When the doctor arrived the patient was conscious and complained of severe headache. He seemed somewhat dull mentally. His temperature and pulse were normal. Three hours later he again had a generalized convulsion which lasted only a few minutes. At this time he was in a semistuporous state, and his temperature was somewhat elevated. He soon lapsed into unconsciousness from which he did not recover. There was no neck rigidity and the extremities were slightly spastic. The leukocyte count was 11,000, urine was normal, and the blood pressure was normal. A spinal tap revealed a bloody fluid under increased pressure. A detailed examination of the fluid and animal inoculation revealed no organisms. By evening the patient's temperature had risen to 104.2° F., pulse 150, and respirations 20. The temperature then varied from 102°–104° F. until the time of death, which occurred the following morning about 1 day after the acute onset, or 3 days after the onset of fatigue and drowsiness. The spinal fluid obtained a few hours before death was identical with the first specimen.

*Autopsy:* Negative except for the brain. The surface of the brain in the right frontal and parietal regions had a reddish appearance. There was a reddish tinge to the spinal fluid at the base of the brain. Sections of the brain revealed a slight amount of pinkish fluid in the right lateral ventricle. Throughout the white substance there were numerous hemorrhages varying in size from those barely visible to some a few mm. in diameter. Some of the largest hemorrhagic areas were in the right frontal and parietal regions where the involvement

extended through the cortex to the surface of the brain. There was no involvement of the cerebellum.

*Microscopic Examination:* The hemorrhages are both diffuse and perivascular. In many areas, especially in the right frontal and parietal regions, large hemorrhages are seen with many smaller ones surrounding them. The brain tissue in and around the larger hemorrhages is destroyed. A fat stain reveals macrophages invading the necrotic tissue. The hemorrhages are numerous in the region of the right lateral ventricle. Many of the vessel walls are damaged and erythrocytes can be seen which have broken out of the vessels into the perivascular spaces. A few polymorphonuclears are discovered scattered among the larger areas of hemorrhage and destroyed brain tissue. No changes can be discovered in the large nerve cells except in the vicinity of the hemorrhages. Occasional areas showing perivascular demyelinization are observed.

Smears and cultures of the brain remained sterile.

CASE 19. Male, aged 10 years. He had always been well. The first signs of illness were chills and vomiting. He was put to bed and for the next few days seemed to improve. On the third day of his illness he complained of headache. That evening he was very irritable and drowsy and by morning could not be aroused. He was admitted to the hospital in this comatose state. Physical examination soon after admission revealed a poorly nourished, unconscious boy. There was no neck rigidity, ocular reflexes were normal and the fundi were normal. The lungs, heart and abdomen were negative. A definite rigidity was noted in moving the upper extremities. None of the deep reflexes was obtained. His temperature was 106.8° F. The white blood count was 21,100 with 81 per cent polymorphonuclears. The urine examination was negative. The spinal fluid was essentially normal except for 10 cells per cmm.

During his stay in the hospital it was observed that the neurological findings were extremely variable. At times the limbs were flaccid, while a few hours later they would be spastic. The reflexes varied in the same manner. His temperature varied, usually remaining above 106°. His respirations became more labored and he died 2 days after admission to the hospital and 4 days after the appearance of the first symptoms.

*Autopsy:* Entirely negative except for the brain. There was no evidence of blood in the cerebrospinal fluid. At the base of the brain over the pons, medulla and adjacent interstices there was a slight hemorrhagic film. The surface of the brain showed no further hemorrhages. On section numerous petechiae were visible throughout the basal ganglia, the cortical regions and the central white matter. The latter showed a slight predominance of lesions. These hemorrhagic areas could have been easily confused with dilated vessels.

*Microscopic Examination:* This shows that many of the suspicious areas are true hemorrhages, while others are merely dilated vessels. Most of the actual petechiae are situated in the white substance of the frontal and temporal regions. Numerous hemorrhages are detected in the pons and medulla also. Only in these latter areas is any round cell infiltration visible. No polymorphonuclears can be found. An occasional ganglion cell seems to be undergoing degeneration, but this finding is too infrequent to be of significance.

CASE 20. Female, aged 7 months. She was first taken ill with a cold. That same evening she lapsed into coma, and her temperature started to rise. She was admitted to the hospital where examination revealed a comatose infant with a temperature of 104.2° F., a slight neck rigidity and normal reflexes. The rest of the physical examination was negative. There were no signs of an upper respiratory infection. The urine was normal and a spinal tap showed the fluid to be under increased pressure with 560 cells per cmm. No bacteria could be found in the smears. Repeated spinal taps showed great numbers of white cells. The red blood count was 2,160,000; white blood cells were 25,000 with 71 per cent polymorphonuclears.

The coma persisted. At times she would have clonic contractions of the extremities most marked on the right side. The reflexes varied and her temperature remained high. She died about 2 weeks after the onset of the illness.

*Autopsy:* The gross appearance of this brain is described in a previous paragraph.

*Microscopic Examination:* The greatest damage is in the left half of the cerebrum, although numerous changes are also seen on the right side. The most marked involvement is in the white substance which contains numerous hemorrhages. These are visible in all sections of the brain but are most extensive in the left frontal and parietal lobes where large areas of brain tissue are completely replaced by red blood cells. Some of the blood vessels are distended with erythrocytes and many more contain collars of red cells. An extensive proliferation of the endothelium of many of the small blood vessels is noted in the frontal regions and around the left lateral ventricle. Destruction of the brain substance is noticeable about many of the larger hemorrhages, as well as around the blood vessels. In these areas there is a great proliferation of the microglia. Sections of the basal nuclei are normal, with the exception of a few dilated vessels. An occasional small hemorrhage is detected in the internal capsule. The pons, medulla, cerebellum and cord are all normal.

Smears and cultures of the brain revealed no growth. Animal experimentation with this brain tissue has been described above.

TABLE IV

*Summary of Cases*

| Case No. | Sex | Age | Duration of illness | First symptoms |
|---|---|---|---|---|
| 1 | M | *yrs.* 33 | 5 hours | Unconsciousness<br>Convulsions |
| 2 | F | 25 | 12 hours | Unconsciousness<br>Convulsions |
| 3 | M | 41 | 4 hours | Unconsciousness |
| 4 | F | 36 | few hours | Found dead |
| 5 | M | 40 | few minutes | Sudden death |
| 6 | F | 14 mo. | 3 hours | Convulsions |
| 7 | M | 25 | 5 days | Dizziness<br>Stupor |
| 8 | M | 44 | 14 days | Headache<br>Stupor |
| 9 | M | 18 | 2 days | Headache<br>Restlessness |
| 10 | M | 35 | 4 days | Malaise<br>Stupor |
| 11 | M | 14 | 3 days | Headache<br>Convulsions<br>Unconsciousness |
| 12 | F | 36 | 3½ days | Headache<br>Unconsciousness |
| 13 | M | 3 | 1 hour | Malaise<br>Stupor |
| 14 | M | 5 | 9 hours | Headache<br>Malaise |
| 15 | F | 55 | 6 days | Headache<br>Convulsions<br>Unconsciousness |
| 16 | F | 11 | 7 days | Headache<br>Convulsions<br>Unconsciousness |
| 17 | F | 2½ | 12 hours | Restlessness<br>Convulsions |
| 18 | M | 20 | 3 days | Headache<br>Convulsions<br>Stupor |
| 19 | M | 10 | 4 days | Headache<br>Stupor |
| 20 | F | 7 mo. | 14 days | Stupor |

## Summary and Conclusions

1. Twenty cases of a peculiar involvement of the central nervous system are reported. We have called this disease hemorrhagic encephalitis, since clinically the patients present a typical picture of encephalitis and pathologically the most striking lesion is a hemorrhagic involvement of the brain.

2. Hemorrhagic encephalitis may be characterized clinically as an acute ailment of the central nervous system occurring in previously healthy young individuals, and manifesting itself by a sudden onset, headache, an abrupt rise of temperature and a rapid loss of consciousness. Convulsions are common, the extremities are spastic, and the reflexes are frequently abnormal and variable. Death ensues in from a few hours to several days after the onset of the illness.

3. The most conspicuous feature of this disease is the pathological picture in the brain. It is chiefly hemorrhagic and predominantly in the white matter. The hemorrhages vary widely in number and size, from extensive extravasations which destroy much brain tissue to tiny perivascular bleedings. In the brains of patients who survive the first few days there are often observed areas of non-hemorrhagic perivascular demyelinization which are invaded by scavenger cells. Consistent specific changes in the ganglion cells have not been observed. An occasional blood vessel shows a slight perivascular infiltration of mononuclears. A few widely scattered polymorphonuclears can be detected in the areas of degeneration. Postmortem study shows that all the organs except the brain are normal.

4. Cerebral hemorrhages may frequently be found in other diseases but by careful clinical and pathological study these can easily be differentiated from true hemorrhagic encephalitis.

5. The brain tissue from 1 case of hemorrhagic encephalitis has proved virulent to rabbits on intracerebral inoculation.

6. On the basis of the present study we are inclined to accept hemorrhagic encephalitis as a clinical entity and believe it is entitled to a definite position in neurological nosology.

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## DESCRIPTION OF PLATES

### PLATE 26

FIG. 1. Section through the brain of a 55 year old female dead of hemorrhagic encephalitis (Case 15). The hemorrhages are almost exclusively of a small discrete type. Note their sharp localization to the white substance of the brain and their relative paucity in the basal nuclei. × 0.8.

FIG. 2. A case of hemorrhagic encephalitis in a child aged 7 months (Case 20). Sections show massive irregular hemorrhages and a marked destruction of brain tissue. The necrotic brain tissue has extended through the cortex to the surface of the brain. × 0.8.

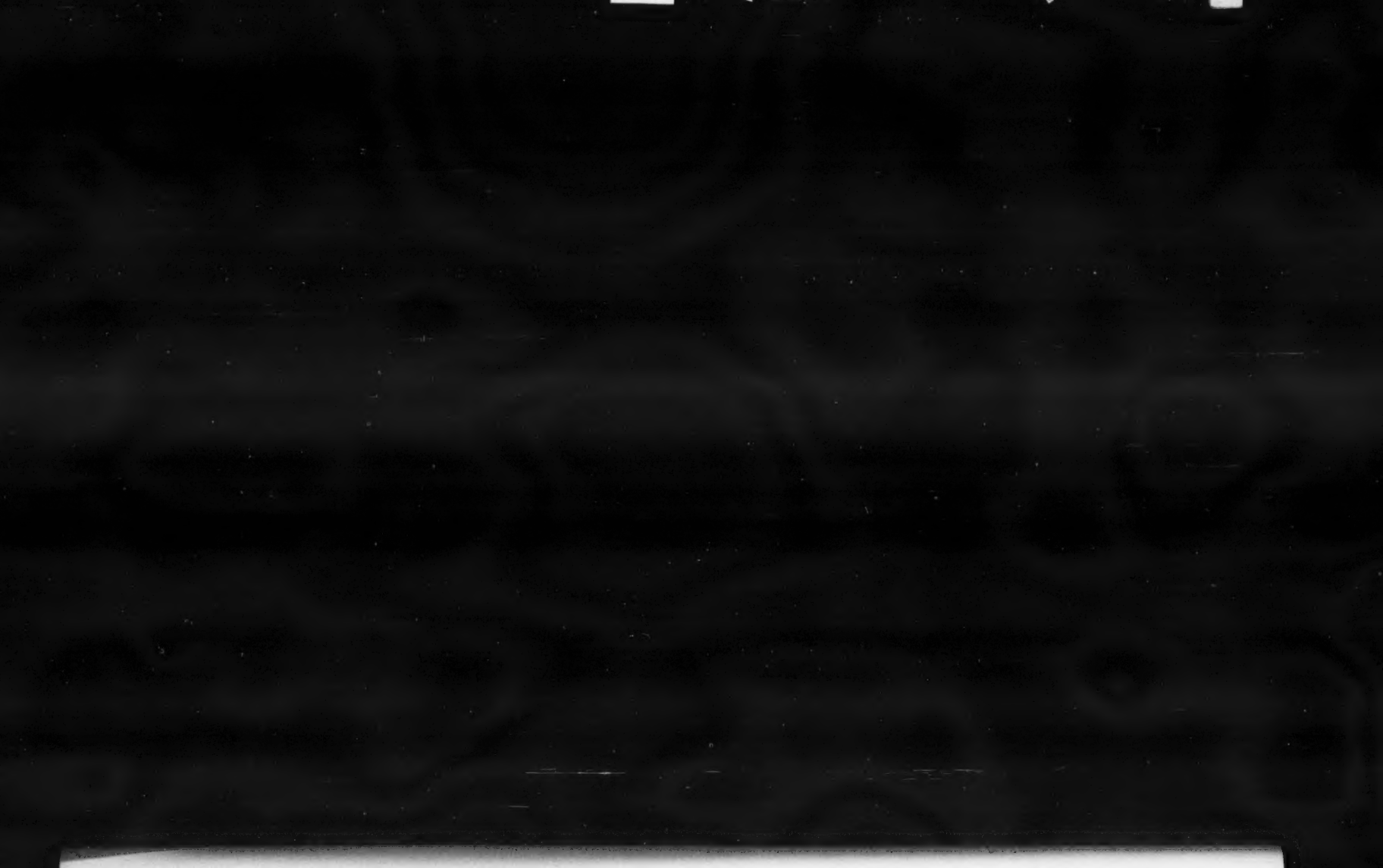

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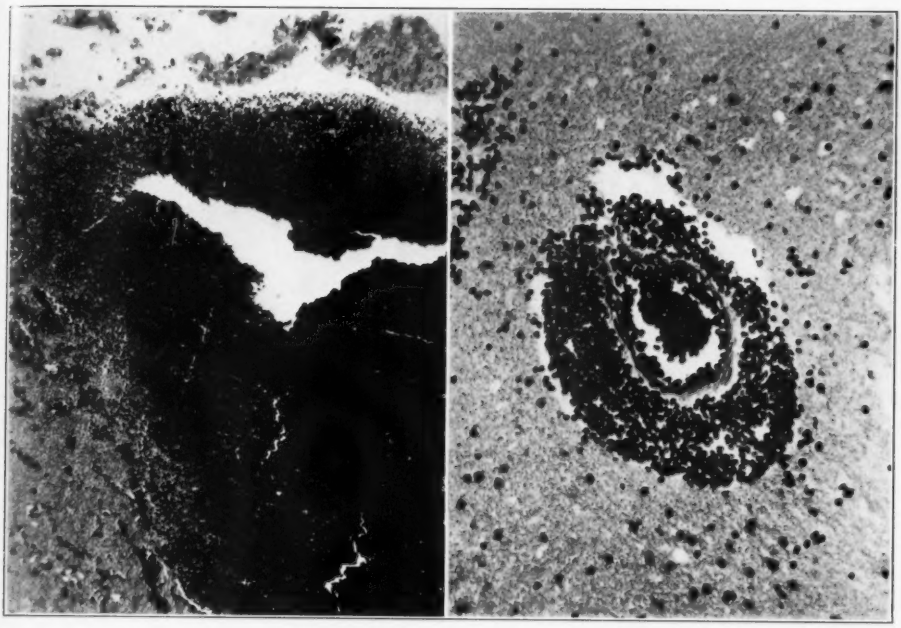
PLATE 27

FIG. 3. A large hemorrhage of the brain from a case of hemorrhagic encephalitis. The red blood cells have extended to the surface of the brain. Numerous smaller extravasations of red cells can be detected around the larger one. Azocarmine stain. × 200.

FIG. 4. Hemorrhagic encephalitis showing rupture of a small vessel with erythrocytes that have apparently passed out into the perivascular space. Note the sharp limitation of the hemorrhage to the perivascular space with only slight involvement of the surrounding brain tissue. Hematoxylin and eosin stain. × 400.

FIG. 5. A "ball" or solid hemorrhage from a case of hemorrhagic encephalitis. Although no vessel is visible in this hemorrhage, the rounded uniform arrangement suggests a vascular origin. Hematoxylin and eosin stain. × 200.

FIG. 6. Hemorrhagic encephalitis showing ring hemorrhages. Note the clear uninvolved center surrounded by a dense ring of erythrocytes. These hemorrhages also have a tendency to remain discrete. They are caused by rupture of the numerous capillaries that surround the larger vessels. Azocarmine stain. × 75.



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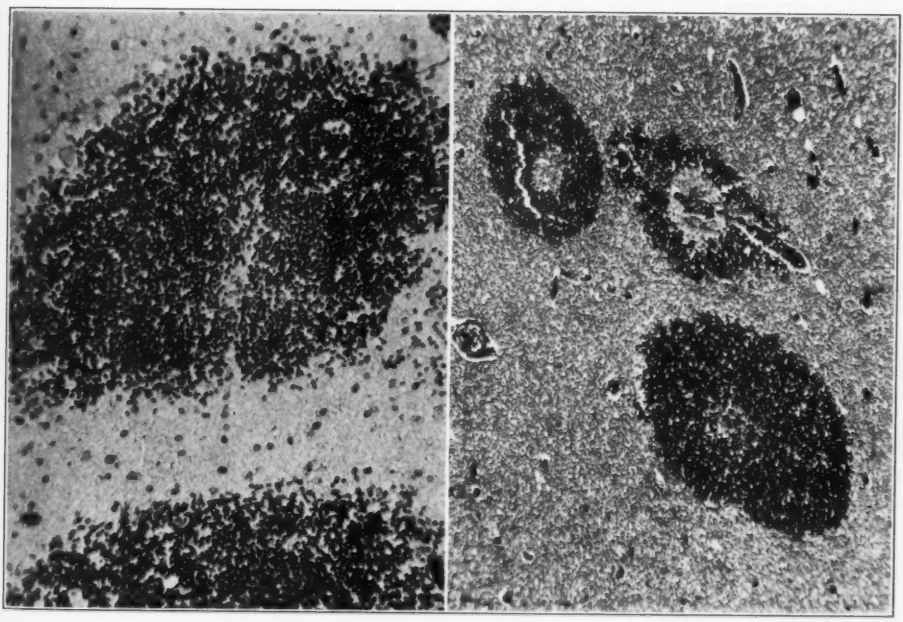

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Baker Hemorrhagic Encephalitis

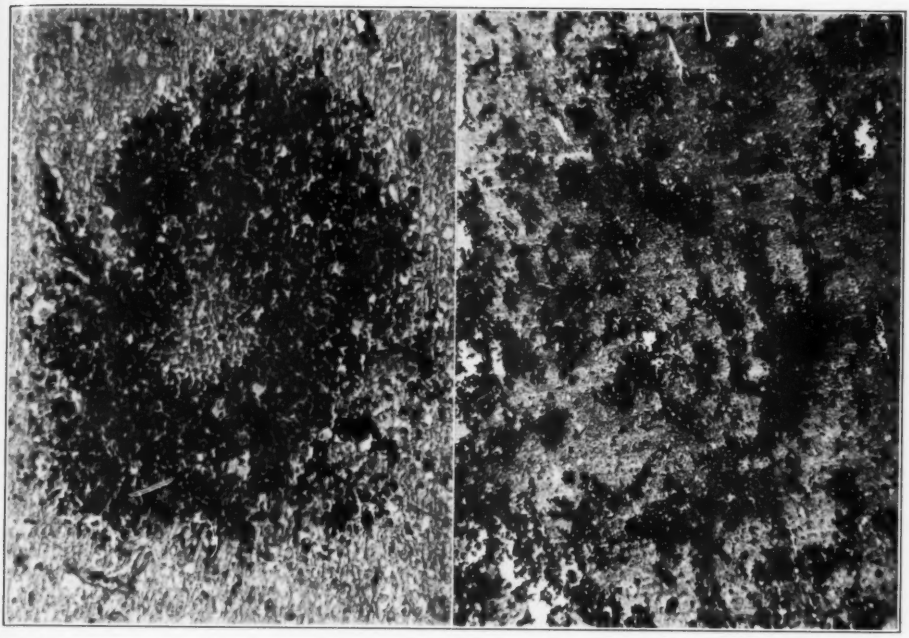
PLATE 28

FIG. 7. Hemorrhagic encephalitis, showing a ring hemorrhage under higher magnification. Note the tendency of the red cells to remain localized. Azocarmine stain. × 200.

FIG. 8. A case of hemorrhagic encephalitis, in which the hemorrhages are diffuse and not limited to the region of the larger blood vessels. These petechiae are small and therefore have caused but slight injury to the surrounding brain tissue. Azocarmine stain. × 200.

FIG. 9. Hemorrhagic encephalitis, showing the thinning out and rupture of numerous brain fibers by a large hemorrhage. Note that an occasional fiber is still intact and passes through the mass of erythrocytes. The invasion of the scavenger cells cannot be seen with this stain. Modified Laidlaw silver stain. × 400.

FIG. 10. Hemorrhagic encephalitis showing complete demyelinization about a cerebral vessel, from a patient who died 6 days after the onset of illness. Note the relative absence of scavenger cells and erythrocytes. There is an increase of glial fibers laid down by the proliferating astrocytes. Iron hematoxylin - Van Gieson stain. × 200.



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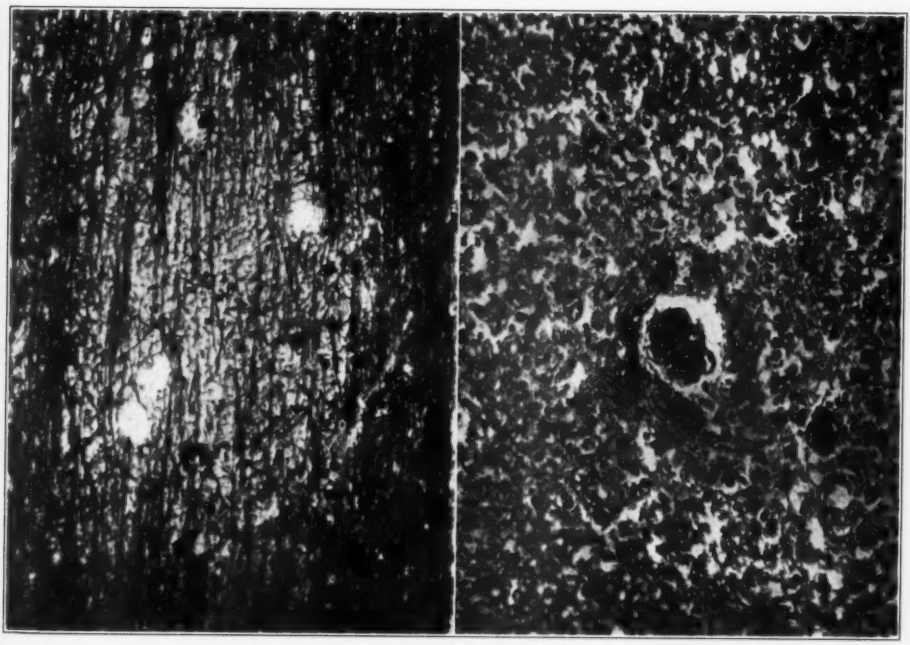

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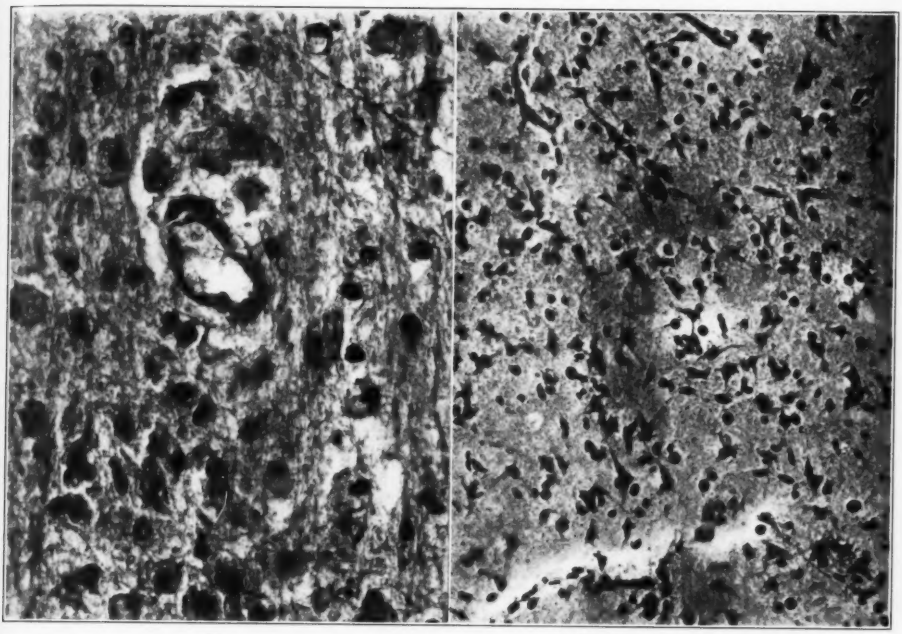
## PLATE 29

FIG. 11. Hemorrhagic encephalitis, early perivascular demyelinization. Note the beginning infiltration of fat-granule cells. There are no free erythrocytes surrounding the vessel. Hematoxylin and eosin stain. × 400.

FIG. 12. Hemorrhagic encephalitis showing a marked increase of microglia in an area of cerebral injury. Many of the cells have just arrived and still possess their wavy branched processes. Others have already changed into "rod cells." No fat-granule cells have, as yet, been formed. Del Río-Hortega's silver carbonate stain. × 400.

FIG. 13. Petechiae in the brain of a patient dead of arsenic poisoning. The hemorrhages are mostly of the ring type. Thrombi are present in the involved vessels. No tissue destruction is apparent. Azocarmine stain. × 400.

FIG. 14. Diffuse extravasations of red cells throughout the brain tissue in a case of purpura. There appears to be no definite localization of the erythrocytes about larger vessels. Azocarmine stain. × 200.



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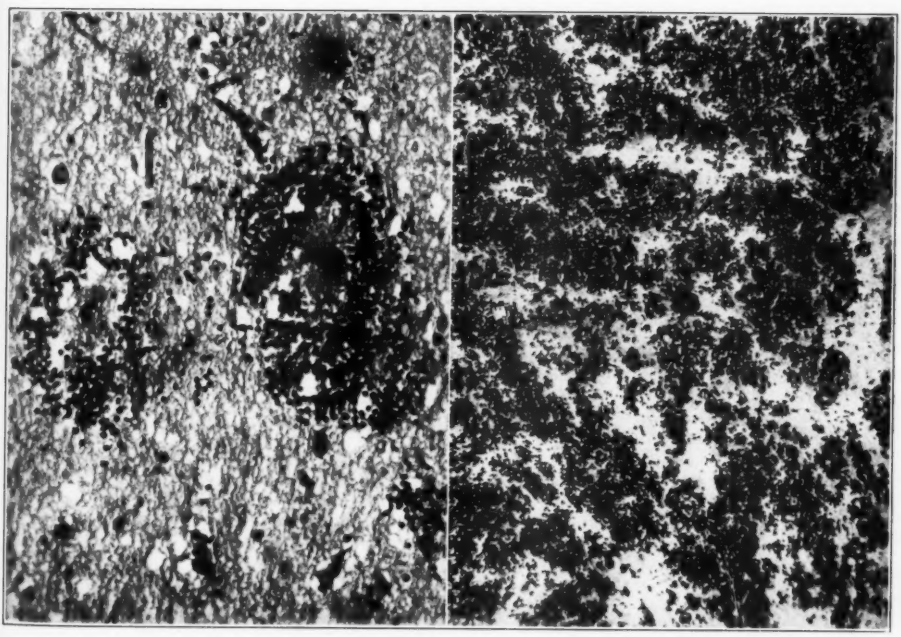

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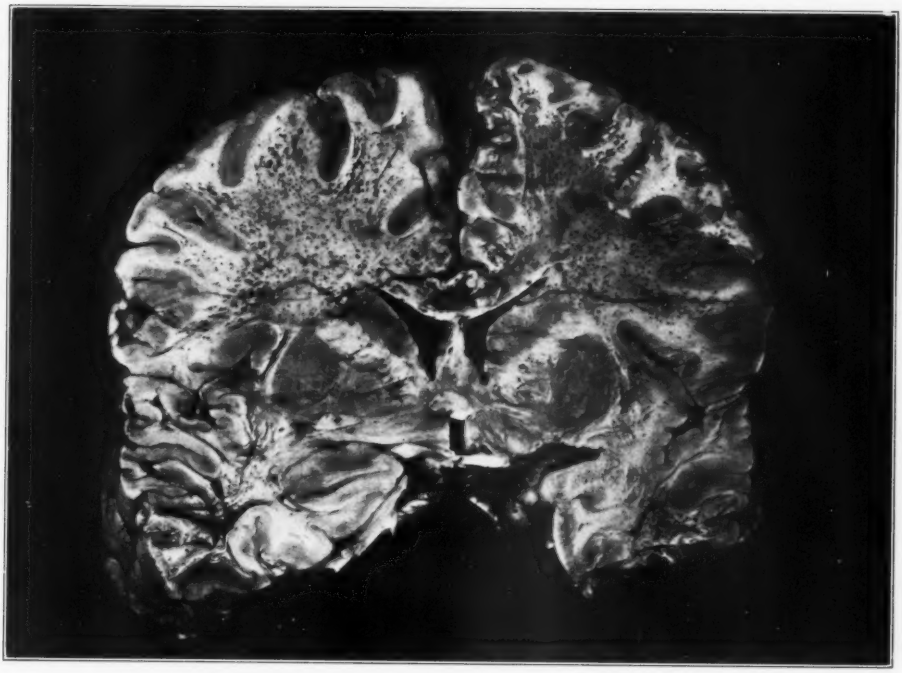
Baker Hemorrhagic Encephalitis

## PLATE 30

FIG. 15. Coronal section through the brain of a patient dead of a bilateral bronchopneumonia. The cerebral tissue is filled with small discrete hemorrhages which tend to be limited to the white substance. The basal nuclei are relatively uninvolved. No gross areas of cerebral softening are visible. × 0.8.

FIG. 16. Traumatic cerebral hemorrhages. Most of the petechiae are found in the white matter. Note the small bruised area in cortex of the brain at the margin of the sagittal suture on the right. There is a tendency for most of the hemorrhages to arrange themselves in tiny groups instead of being disseminated throughout the tissue. × 0.8.



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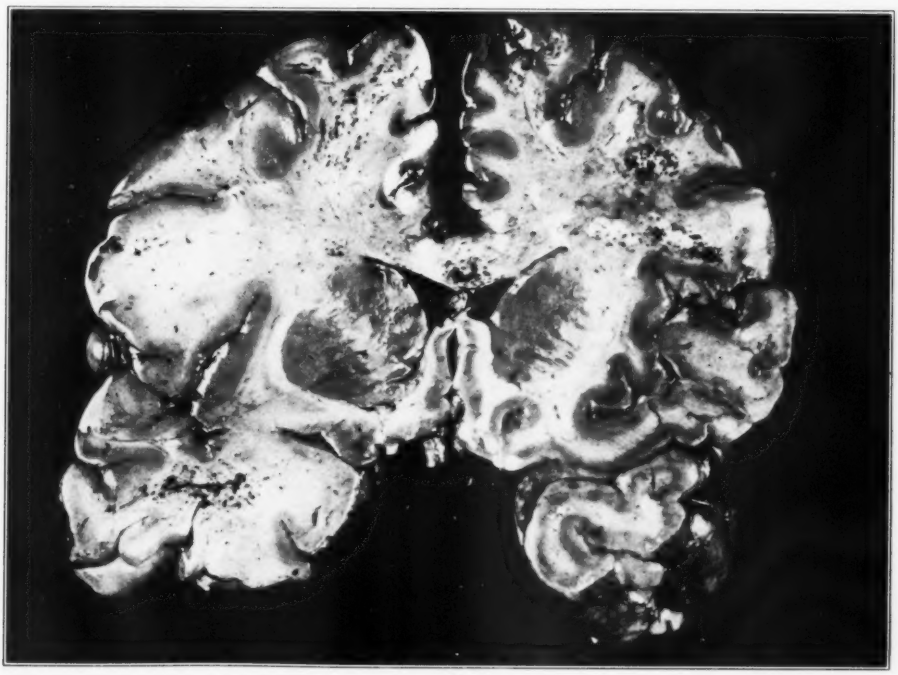

16

# DISTRIBUTION OF NUCLEAR INCLUSIONS IN WILD ANIMALS *

E. V. Cowdry, Alfred M. Lucas and Herbert Fox

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The viruses that are most destructive receive the closest attention. But biologically the less pathogenic ones, the presence of which is not revealed by distinctive clinical symptoms, are equally important to those who wish to understand the place in nature of these elusive organisms or substances. The discovery of the latter has been largely a matter of chance. In 1920 Jackson [1] reported intranuclear inclusions, which she called protozoan parasites, in the salivary glands of guinea pigs, explaining that they were observed in examinations made for an entirely different purpose. We now know that they are caused by a virus. During the routine study of the tissues of rats in a large dietary experiment, Thompson [2] discovered somewhat similar inclusions also in the salivary glands. In the course of investigations on Rift Valley fever, Findlay [3] found intranuclear inclusions in the liver cells of mice which showed no symptoms of disease and were caused by a hitherto unrecognized mouse virus. Many other instances of chance favoring the prepared mind might be cited.

If we try to plot out the distribution of nuclear inclusions which have been proved experimentally to be of virus etiology and others under suspicion in the vertebrate series, we find them in 2 fish, 1 amphibian, no reptiles, 4 birds and at least 11 mammals. This list includes only the species in some individuals of which they naturally occur. It does not include a considerable number of other species in which inclusion formation can be induced by injection of viruses foreign to them. Impressed by the need for more data on the distribution of intranuclear inclusions, and possibly of viruses, particularly in wild animals, the Rectors [4] made a short survey of the tissues of such species in the vicinity of St. Louis and found a remarkable case of their development, without symptoms, in the salivary glands of common moles. The purpose of this paper is to report briefly a

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more detailed survey chiefly of the kidneys of mammals and birds from the pathological service of the Zoological Society of Philadelphia.

## Material

This included 165 animals of which 78 were mammals and 87 were birds. The mammals belonged to 58 species distributed as follows: *Artiodactyla* 16, *Primates* 10, *Xenarthra* 1, *Rodentia* 8, *Carnivora* 21 and *Marsupialia* 2. The birds comprised 62 species as follows: *Passeriformes* 5, *Strigiformes* 2, *Coraciiformes* 1, *Piciformes* 1, *Psittaciformes* 20, *Columbiformes* 2, *Ralliformes* 3, *Galliformes* 4, *Accipitriformes* 9, *Anseriformes* 8, *Ardeiformes* 4, *Struthioniformes* 1, *Balearicifórmes* 1 and *Phoenicopteriformes* 1. The majority, negative as far as inclusions are concerned, are listed later by themselves and the few positive are given in Table I.

Most of the tissues were fixed in formalin or Zenker's fluid and sections were colored routinely with hematoxylin and eosin. In special cases Giemsa's stain was also employed. By reference to the number accompanying each specimen complete clinical and pathological reports could be secured from the records of the Zoological Society. A large collection of specimens showing nuclear inclusions in virus diseases was available for comparison in the Anatomical Laboratory of Washington University.

## Observations

Search was made for the type A and B inclusions of Cowdry.[5] Under type A are grouped those caused by the viruses of herpes, yellow fever, mad itch, fox encephalitis and so on; and under type B those in Borna disease, poliomyelitis, and so on. In both there is an increase in acidophilic material in the nucleus but there the similarity ends. Type A inclusions are formed by the accumulation in the nucleus of granular acidophilic material and the margination on the nuclear membrane of all the basophilic nuclear substance. At a certain stage in their development a clear space is interposed between the central, acidophilic and the peripheral basophilic materials. The nucleoli are altered, move to the nuclear membrane, disappear and the inclusion-laden nuclei disintegrate.

Type B inclusions, on the contrary, are usually spherical, often hyaline, droplet-like bodies which make their appearance in nuclei

that otherwise look fairly normal. The basophilic chromatin is not marginated in the same way but when the inclusions become very large, as they sometimes do, it is pushed away toward the nuclear membrane. The nucleoli persist for a longer time and nuclear disintegration is less marked.

To recognize well developed inclusions of either type is not difficult. It is the border line cases that give trouble. Normally the nuclei of the renal tubules of mammals and birds are rounded bodies of fairly uniform size. One, occasionally more, nucleoli are present and are the only nuclear structures visible in them in the living unstained state. But it is with fixed tissues that we have to deal. In them the nucleoli generally color with basic dyes, but they are really amphinucleoli, for they contain some acidophilic as well as basophilic material. The association of the two components is not always the same. It is when the basophilic material is mixed with the acidophilic that the nucleolus as a whole colors blue with Giemsa or hematoxylin and eosin. Frequently the basophilic component is applied rather unevenly on the surface of acidophilic substance, which is more definitely spherical in form and acts as a kind of core (Figs. 2 and 16). More rarely it becomes detached altogether from the acidophilic mass, in which case the latter is commonly called an acidophilic nucleolus, or plasmasome, but this is not illustrated in our figures. The prefix, plasma, indicates something staining with plasmatic, acid dyes in contrast to nuclear, basic ones. In addition to the nucleolus the nuclei contain irregular masses and strands of basophilic material which are generally more marked as the basophilic nuclear membrane is approached. A small amount of acidophilic material can also be distinguished in the nucleoplasm. Sometimes it appears as a thin, more or less homogeneous deposit in which condition it is represented in gray near the nucleoli in Figures 1 and 2. It may, however, appear in the form of fairly discrete particles like those which make up inclusions caused by viruses. Its relation to the acidophilic nuclear core is not known. Microincineration shows that the latter is much richer in mineral constituents, but this difference may be only one of degree conditioned by the greater density of the nuclear core. In the nuclei of the convoluted tubules the extranucleolar acidophilic material and the nucleoli are more noticeable than in the nuclei of the collecting tubules. In the birds' kidneys they are slightly more prominent than in mammals.

But the tissues examined were not normal. They came from an extensive autopsy service and the nuclei exhibited a wide variety of modifications. We shall eliminate first those that we do not consider to have any definite bearing on our problem.

Increases in acidophilic material to the degree illustrated in gray in Figures 1 and 2 were listed as negative. As was inevitable, some of the tissues showed postmortem autolysis. In such cases the acidophilic nuclear material referred to becomes more prominent (Fig. 5) and other changes occur which will be described in detail by Lucas and Cowdry [6]; but the alteration sweeps through the tissue fairly uniformly in the case of the epithelial cells present and for this reason can easily be distinguished from the effect of virus action which is more localized, and generally, but not always, accompanied by characteristic lesions.

Hypertrophy of individual nuclei (Fig. 18) and of groups of nuclei was very commonly seen without either type A or B inclusions. It was observed in 18 species of birds and was most marked in a South American porcupine. In 5 mammalian species and in 1 bird this was accompanied by margination of basophilic chromatin. Margination alone without increase in central acidophilic material (Fig. 6) was observed in 9 mammalian species and 4 avian ones. Sometimes the nucleoli were enlarged (Fig. 16).

Though alterations such as these were noted in some of the following specimens, no definite intranuclear inclusions suggestive at all of virus action were detected. The specimens are listed because any study of distribution must take into consideration negative findings. Only the kidneys were examined, unless other organs are mentioned. The numerals in brackets indicate the number of individuals of a given species studied when this exceeded one.

### Mammals

*Artiodactyla*
- Klipspringer
- Llama
- Indian buffalo
- Blesbok
- Himalayan thar
- White tailed gnu
- Bison (3)
- American elk
- Western water buck
- Apis deer
- Japanese sika deer
- Hog deer
- Central American deer (2)
- Virginia deer
- Red deer
- Pigmy hippopotamus

*Primates*
- Green monkey (2)
- Kra macaque
- Orang utan
- Hocheur monkey
- Weeper cebus (2)
- Common marmoset
- Silky marmoset

*Xenarthra*
- Long haired armadillo

*Rodentia*
- Canada porcupine (3)
- Porcupine
- Capybara
- Coypu rat
- Prairie dog
- Prevost's squirrel
- Gray squirrel (2)

*Carnivora*
- Sea lion
- Himalayan bear
- European brown bear
- Black bear
- European badger
- Mink (2)
- Polecat
- Otter
- White nosed coati (2)
- Ring tailed coati
- Crab eating raccoon
- Raccoon (3)
- Coyote
- Red fox
- Carpathian fox
- Jackal
- Two spotted paradoxure
- African civet
- Wild cat
- Caracal lynx
- Eyra cat (2)

*Marsupialia*
- Common opossum (6)
- Red kangaroo

BIRDS

*Passeriformes*
- Canary
- American robin
- European jay
- Wild grackle (brain only)
- Common crow (2)

*Strigiformes*
- Barn owl
- Spectacled owl

*Coraciiformes*
- Abyssinian ground hornbill

*Piciformes*
- Cuvier's toucan

*Psittaciformes*
- Undulated grass parrakeet
- Parrakeet
- Blue and yellow macaw (liver only)
- Red and blue macaw
- Red sided eclectus
- Salles amazon
- White fronted amazon (2) (also liver and lung)
- Yellow fronted amazon (3) (also liver and lung)
- Salvin's amazon
- Green cheeked amazon (2) (also liver)
- Golden naped amazon
- Festive amazon
- Levaillant's amazon (7) (also liver and lung)
- Wild parrots (6) (also brain)
- Red vented parrot
- St. Vincent's parrot
- Lesser sulphur crested cockatoo
- Sulphur crested cockatoo

*Columbiformes*
- Barbary turtle dove

*Ralliformes*
Common coot
Purple gallinule
Florida gallinule

*Galliformes*
Common peafowl (2)
Rain quail
Vulturine guinea fowl

*Accipitriformes*
Rupple's vulture
Abyssinian vulture
Cooper's hawk (2)
Red shouldered hawk
Goshawk
Marsh hawk
Red tailed hawk (2)
Batleur eagle
Bald eagle

*Anseriformes*
Gargany teal
Muscovy duck
Mallard duck (2)
Lesser white fronted goose
Hybrid goose
Egyptian goose

*Ardeiformes*
White necked stork
White stork
Scarlet ibis (2)
Straw necked ibis

*Struthioniformes*
Somali ostrich (2)

*Balearicifformes*
Demoiselle crane

*Phoenicopteriformes*
Ruddy flamingo

The intranuclear inclusions that we desire to report are listed in Table I.

Type A inclusions, found in the kidneys of two Guatemalan amazons (Figs. 9–15), were interesting because they exhibited points of resemblance to the inclusions caused by the yellow fever virus. Compare Figures 9 and 10 with Cowdry and Kitchen's [7] Figure 16, and Figure 11 with their Figure 24. In both, the nuclear inclusions are made up of sharply outlined particles of fairly uniform size. They appear in the form of clumps in the zone intermediate between the nucleolus and nuclear membrane. But in the Guatemalan amazon fewer nuclei show them and the condition did not lead to necrosis. In amazon No. 10602 there were approximately 1.164 inclusion-laden nuclei per oil immersion field and in No. 10240, 0.125. The sections were about 8 microns thick. A simple calculation gives the incidence of inclusions in the sections more accurately, in the first at 65.6 per sq. mm. and in the second at 7.07. In addition to the kidneys the liver, lung, testis, epididymis, striated and heart muscle of amazon No. 10602 and the liver, lung, testis, epididymis, pancreas, spleen and intestine of amazon No. 10240 were examined without finding any more type A inclusions. Type B were, however, found abundantly in the lungs of No. 10602 (Figs. 14 and 15), but were absent in the lungs of No. 10240, despite the presence in both of similar

lesions of advanced anthracosis. Nothing in the history of either animal suggests a virus infection. The autopsy reports were:

No. 10602: Injury and malnutrition; edema, congestion, hemor-

TABLE I

| Animal | Type A inclusions | Type B inclusions | Figures |
|---|---|---|---|
| *Mammals* | | | |
| *Artiodactyla* — Red deer | | + | |
| *Primates* — Mongoose lemur | | + | 3 |
| " — Kra macaque | | + | |
| " — Rhesus macaque | | + | 4 |
| " — Lion tailed macaque | | + | |
| *Rodentia* — South American porcupine | | | |
| *Birds* | | | |
| *Piciformes* — Cuvier's toucan (liver, lung, pancreas, intestine, spleen — negative) | | + | 7 and 8 |
| *Psittaciformes* — Guatemalan amazon, 10,240 (liver, lung, pancreas, intestine, testis, epididymis, and spleen — negative) | + | | 9 and 10 |
| " — Guatemalan amazon, 10,602 lung | + | | 11, 12 and 13 |
| (liver, striated and cardiac muscle, testis and epididymis — negative) | | + | |
| " — Black crested cockatoo | +? | | 17 |
| *Columbiformes* — Wonga Wonga pigeon | | + | 18 |
| *Galliformes* — Silver pheasant | | + | |
| *Accipitriformes* — Marsh hawk | | + | 20 |
| *Anseriformes* — Ceropsis goose | | + | 21 |
| " — Spur winged goose | | + | |

rhage and anthracosis of lungs; myocardial degeneration and chronic endocarditis (?), atrophy of spleen and thyroid; atrophy and fibrosis of adrenal; pigmentation and hydropic degeneration of liver; atro-

phic enteritis, atherosclerosis (carotid and aorta); hyperplasia of bone marrow.

No. 10240: Pigmentation, passive congestion and multiple abscesses of liver (Gram-negative bacilli in smears); hyperplasia of bone marrow; acute necrotizing enteritis; hydropic degeneration of pancreas; cloudy swelling of kidney; edema, congestion and abscess formation of lungs; pigmentation, diffuse hyperplasia and myeloid metaplasia of spleen.

The nuclear inclusions in the black crested cockatoo were less noticeable and it is doubtful whether they merit inclusion in type A, although the nucleus illustrated in Figure 17 could not itself be distinguished from one affected by the virus of herpes for example. It is the infrequency of such nuclei, coupled with the absence of tissue reaction and the unsatisfactory way that the tissue stained, which makes the diagnosis doubtful.

Nuclei containing type B inclusions were spread quite widely in the preparations among other nuclei which showed no inclusions; but in the marsh hawk the change was sharply localized, being limited to the nuclei of a single collecting tubule (Fig. 20). These type B inclusions are clearly of more frequent occurrence than those of type A and may (Figs. 4, 8 and 20) or may not (Figs. 3, 7, 14, 15 and 21) be accompanied by nuclear hypertrophy; whereas the type A inclusions in the amazon and cockatoo did not make their appearance in particularly enlarged nuclei; the largest is represented in Figure 13. No characteristic lesions, either infiltrative, proliferative or degenerative, were found with the type B inclusions, neither did the clinical history or the autopsy findings give any reason to believe that a virus was operative. Yet some of these type B inclusions were as large and conspicuous as any reported in the literature. We compared them particularly with inclusions in the kidneys of sewer rats, of which specimens were very kindly sent to us by Dr. E. Hindle.[8]

The crystalline inclusion represented in Figure 19 was unique. Others like it were not found even in the same preparation. It is quite different in appearance from the large intranuclear acidophilic crystals first reported by Szymonowicz and Macallum and found also by Cowdry and Scott [9] in the livers of dogs.

Before attempting to discuss the possible significance of these observations we wish to report the results of a search for nuclear

inclusions in kidney specimens from 1012 human autopsies courteously loaned to us by Dr. H. Gideon Wells of Chicago. No type A inclusions were found. Type B inclusions were seen in only 17 kidneys, or 1.67 per cent, as contrasted with 14 out of 163 animals, or 8.58 per cent.

But the incidence of nuclear inclusions may not be so much lower in the human series than in the wild animals as the figures indicate. If the search for them in the humans had been equally thorough a few more might have been found. The sections of the human kidneys had all been well stained with hematoxylin and eosin, which is the most satisfactory method for inclusions, because of color contrast and permanency, but some of them were rather too thick. It is more difficult to identify inclusions by focussing up and down through entire nuclei than in preparations about 5 microns thick in which many nuclei are cut in section. But none of the sections were so thick that they could not be easily studied with a 3 mm. oil immersion objective. Postmortem changes were rather more frequent in the human series. In such cases, the shrinkage of the nuclei and alteration in staining reaction would have interfered with the identification of inclusions, particularly those of type A, if not well developed.

On the other hand pathological lesions were much more numerous and varied in the human than in the wild animal series. With greater frequency in functional disturbance, one would expect a somewhat higher incidence of inclusion formation quite irrespective of whether they are caused by viruses or cellular environments unusual in osmotic or other features. Indeed, the remarkable rarity of nuclear inclusions in the human series shows that, in the kidney at any rate, they are not ordinary, commonly encountered nuclear degenerations. Comparison of the 14 kidneys, in which they were seen, with the others failed to reveal any distinctive pathological process. None of the inclusions were so large and noticeable as those observed in some of the wild animals and others in preparations of frog and rat kidneys kindly sent to us by Dr. B. Lucké and Dr. E. Hindle respectively (see Lucké,[10] Figs. 14 and 15, and Hindle [8]). Neither were they so conspicuous as the inclusions reported in the kidneys of fetuses and young children by many authors (see Farber and Wolbach [11]). The kidneys that we examined were almost entirely from adults. It is possible that such inclusions, though present

earlier, had disappeared, or that a geographic factor of some kind operates, as suggested by Farber and Wolbach, and that for some unknown reason this factor is less widespread in the Middle West.

## Discussion

This examination of many specimens of the kidneys of wild animals and humans has been a fatiguing but very profitable experience. It has not brought to light a single instance of inclusions that we care to attribute definitely to virus action. Those which most nearly qualify were the A inclusions in the Guatemalan amazon and the B inclusions in the marsh hawk. Neither was accompanied by an infiltrative tissue reaction. It is clear that type A are less common nuclear modifications than type B. How are we to explain their formation?

Obviously about all we can do is to mention some of the possible factors. Wells [12] states that "it is probable that chemically the differences between nucleus and cytoplasm are quantitative rather than qualitative." This view is supported by recent studies on microincineration which show that nuclei are richer in mineral constituents than was formerly supposed (Scott [13]). Chromatin holds our attention because it stains vividly and on account of its great physiological significance, but it is one of many nuclear components. Chemically, chromatin is a protein salt of nucleic acid. According to Mathews,[14] "the nucleic acid is apparently the same, or at any rate closely similar in all the different cells examined; but the protein base appears to be characteristic of the cell." The firm, jelly-like consistence of most nuclei he attributes to the gelatinizing property of solutions of nucleic acid salts. The nucleic acid is basophilic for it combines with "basic" dyes. That "basic chromatin" carries a negative electrical charge has been shown by McClendon.[15] When cells are placed in an electric current he observed the actual pushing out of the nuclear membrane toward the anode by pressure of the basic chromatin. Acidophilic material carries, on the contrary, a positive charge. The outstanding feature of the formation of type A inclusions is a change involving the entire nucleus by which the acidophilic material, perhaps the protein, protamin or histon base of the nucleic acid salt, becomes separated from the basophilic nucleic acid and accumulates in the center, whereas the acid moves to the

periphery of the nucleus. But the acidophilic substance may be only partly or not at all of chromatinic origin. Other nuclear components than chromatin may be involved and there is a possibility that some of it may enter the nucleus from the surrounding cytoplasm, for there is usually some hypertrophy which must be due to intake of extraneous material, though it may simply be water.

At first sight one gains the impression that an alteration of this sort might result from the action of a nuclease. Van Herwerden [16] was able to remove selectively basophilic components from several types of cells by allowing a nuclease to act on sections of alcohol, or hot water, fixed tissue. We experimented with a nuclease kindly prepared for us by Dr. D. J. Kooyman. This we injected into the living epidermis, because we thought that in an avascular situation we might secure a maximum change. But stained sections failed to show any sign of the development of type A inclusions. Moreover, in our studies on postmortem autolysis chromatin is broken down, presumably by nuclease, but inclusions are not formed. Lee,[17] working in this laboratory, has been more nearly successful in his investigation of osmotic factors producing acidophilic inclusions which very closely resemble those caused by viruses. The process, whatever it is, of type A inclusion formation ordinarily goes on to complete nuclear disintegration and cellular necrosis. It is generally accompanied by a local invasion of phagocytes.

Type B inclusions occurred more frequently, both in the wild animals and humans. The chromatin is not divided in quite the same way into central acidophilic and marginating basophilic fractions. When they are small the nuclear structure about them is not modified, except for the appearance of a delicate halo. When they increase greatly in size the contents of the nucleus are crowded toward the nuclear membrane. As with beginning type A inclusions, it is not possible to draw a definite line of distinction between the inclusions themselves and acidophilic material normally present in small quantities in the nuclei. The nuclear change is less radical than in type A. It has the appearance of developing more slowly and the terminal stage of necrosis is seldom seen. This may explain why type B inclusions often occur without an associated tissue reaction, toxic substances perhaps not being liberated to the same degree as in the development of A inclusions. We do not deny that type B inclusions may be the result of virus action but we think that they

may be caused directly by other factors as well, or secondarily by viruses activating or influencing these other factors. In estimating the probability that any given type B inclusions are due to virus action several considerations are important.

The first is the extent of deviation from normal. When the inclusions are of small size, consisting only of droplets of acidophilic material in nuclei whose cells otherwise look as usual, one is inclined to dismiss them as of little if any significance from the point of view of viruses. Another feature that leads to scepticism is uniformity in distribution of the inclusions in practically all cells of the same sort in a preparation; for, as already stated, the action of viruses is generally limited to relatively small foci and unequal in degree, some cells being altered slightly and others more severely, as if they had been attacked one after another.

Inclusions of this type B are only exceptionally marked by a tissue reaction detectable by routine techniques, by which we mean necrosis of cells, infiltration by phagocytes, fibrosis and so on. It is possible that the application of special cytological and microchemical methods might reveal alterations in the neighboring epithelial cells and we exclude arbitrarily, in specifying the tissue reaction, hypertrophy and other modifications in the inclusion-laden cells themselves. A tissue reaction of this kind was not a noticeable accompaniment of type B inclusions in either our wild animal or human series. It may have occurred to a mild degree and have disappeared, or the inclusion formation in any particular locality may perhaps be secondary to considerable increase in virus elsewhere and transport of the virus to the area by the blood stream. This may apply also to certain type A inclusions. A dog which had been inoculated with fox encephalitis virus showed in its kidney (given to us by Dr. R. G. Green [18]) inclusions limited to the renal glomeruli and there was no tissue reaction. But the affinity of this virus is primarily for endothelium. Moreover, the inclusions in fetuses and young children are often devoid of tissue reaction, as noted by Farber and Wolbach.[11]

Early type B inclusions may be of the same size as nucleoli or considerably smaller. One or more of the following distinguishing features can generally be made out. (1) Clear halos common about the inclusions are rare or absent about the nucleoli. (2) The inclusions are not definitely placed in the nuclei and of limited number like the nucleoli. (3) When several inclusions occur in a single nu-

cleus, they often exhibit a gradation in size from bodies much smaller than nucleoli to considerably larger ones. (4) They are usually wholly acidophilic, whereas the nucleoli may color with both acid and basic dyes or consist of an acidophilic core on which basophilic material is plastered.

Further investigations may bring to light other differences. Nucleoli differ from type A inclusions in the possession of large amounts of mineral.[19, 20] We have incinerated the type B inclusions in Hindle's sections of rat's kidneys and wish to report very little mineral, but the specimens were not fixed by the best method for microincineration. We have no data for other type B inclusions but we think it likely that this difference from nucleoli will hold. Nucleoli are known to be very compact structures. In the nerve cells of some lower forms they settle in the lowest parts of the nuclei by their own weight and most histologists have seen instances of nucleoli carried right out of the nuclei by the microtome knife. A careful comparison of both types of inclusions with nucleoli and basophilic chromatin in centrifuged cells is indicated.

When, on the other hand, type B inclusions are localized in distribution, are very large, and the containing nuclei are much distended, we entertain the possibility of virus action and await experimental proof. This is the status of the inclusions in the kidney of the marsh hawk and in the kidneys of sewer rats of Hindle. Bodies difficult to distinguish morphologically from inclusions of type B apparently occur normally in the cells of the vesicula semenalis of certain mammals and humans, [21-24] and in those of the nucleus supraopticus and paraventricularis of the midbrain of many vertebrates and humans.[25-28] In both localities they are interpreted as phases in the elaboration of nuclear secretions, for which, however, the evidence, in our opinion, is insufficient. But their similarity to inclusions in other tissues, which some have attributed to virus action, inspires caution.

How type B inclusions are formed remains to be determined. Splitting of the nucleic acid salt of protein is not a conspicuous feature. When first they begin to grow, the internal organization of the nuclei is not lost. They seem to be passive accumulations of substance, the nature of which awaits chemical analysis. All we know at present is that, like the type A inclusions, they contain little or no thymonucleic acid and are not of fatty nature. They may conceivably be produced by faulty elimination of nuclear material or by the entry of extraneous material in unusual amounts. Either might be

occasioned by a modification in the permeability of the nuclear membrane, which in turn might result directly or indirectly from the operation of a virus or simply from a functional derangement of common occurrence in some tissues and very rarely seen in others, depending upon their intrinsic attributes.

## Summary

Type A inclusions resemble those of herpes and usually: (1) exhibit a change which sweeps through the entire nucleus whereby acidophilic material accumulates in the center to form the inclusion and basophilic material marginates on the nuclear membrane; (2) lead to complete disintegration of the injured cells, and (3) are accompanied by a noticeable tissue reaction. Inclusions of this kind were seen only in the kidneys of 2 Guatemalan amazons. In so far that each inclusion was made up of clumps of discrete acidophilic particles and the nucleoli were not displaced early in the process, they look quite like the intranuclear inclusions caused by the yellow fever virus, but they were rather evenly distributed in the tissue and were not accompanied by distinctive lesions.

Type B inclusions resemble those in Borna disease and usually: (1) develop as local accumulations of acidophilic material in nuclei, the remaining parts of which at first show no other modifications; (2) crowd all other nuclear materials toward the nuclear membrane as they increase in size; (3) do not lead to extensive nuclear disintegration or to severe accompanying tissue reactions. These were more widely distributed. They were found in the lungs of one of the Guatemalan amazons and in the kidneys of 7 out of 62 species of birds, 6 out of 58 species of mammals and 17 out of 1012 individual humans.

Acidophilic nuclear material is normally present in small amounts in the nuclei of renal epithelial cells. There is no sharp line of distinction between it and inclusions of either type. It is the degree of change that raises the question of virus etiology. When the inclusions are (1) so conspicuous that they can be seen without the aid of oil immersion objectives, (2) localized in distribution, and (3) related to marked lesions, one looks for a virus. But no type A inclusions, and especially no type B ones, which are so much more common, should be regarded as pathognomonic of virus action without experimental proof.

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## DESCRIPTION OF PLATE

### PLATE 31

The drawings of selected nuclei were made with camera lucida at a magnification of 2400 diameters. Nuclear material, which was acidophilic and colored red in the original stained preparations, is represented in shades of gray and basophilic material, which was blue, in black or very dark gray.

FIG. 1. *Canada porcupine.* Convoluted tubule. A little acidophilic material is shown near the nucleolus.

FIG. 2. *Straw necked ibis.* Convoluted tubule. Slightly more acidophilic material. Nucleolus with an acidophilic core.

FIG. 3. *Mongoose lemur.* Convoluted tubule. Type B inclusion.

FIG. 4. *Rhesus macaque.* Convoluted tubule. Type B inclusion; basophilic chromatin not marginated, just pushed aside; nuclear hypertrophy.

FIG. 5. *Prairie dog.* Convoluted tubule. Marginal clumping of chromatin with central basophilic granules.

FIG. 6. *Red kangaroo.* Convoluted tubule. Margination of basophilic chromatin alone without inclusion formation.

FIG. 7. *Cuvier's toucan.* Convoluted tubule. Type B inclusion surrounded by a distinct halo.

FIG. 8. *Cuvier's toucan.* Convoluted tubule. Small type B inclusion with marked nuclear hypertrophy.

FIGS. 9–10. *Guatemalan amazon.* (*No. 10240*). Convoluted tubule. Two stages in development of type A inclusions leading to complete margination of basophilic chromatin.

FIGS. 11–13. *Guatemalan amazon* (*No. 10602*). Convoluted tubule. A further stage in inclusion formation (11). Coalescence of acidophilic inclusion particles in a shrunken and a hypertrophied nucleus (12 and 13).

FIGS. 14 and 15. Same. Type B inclusions in epithelial cells of the lung.

FIG. 16. *Yellow fronted amazon.* Convoluted tubule. Nucleolar hypertrophy.

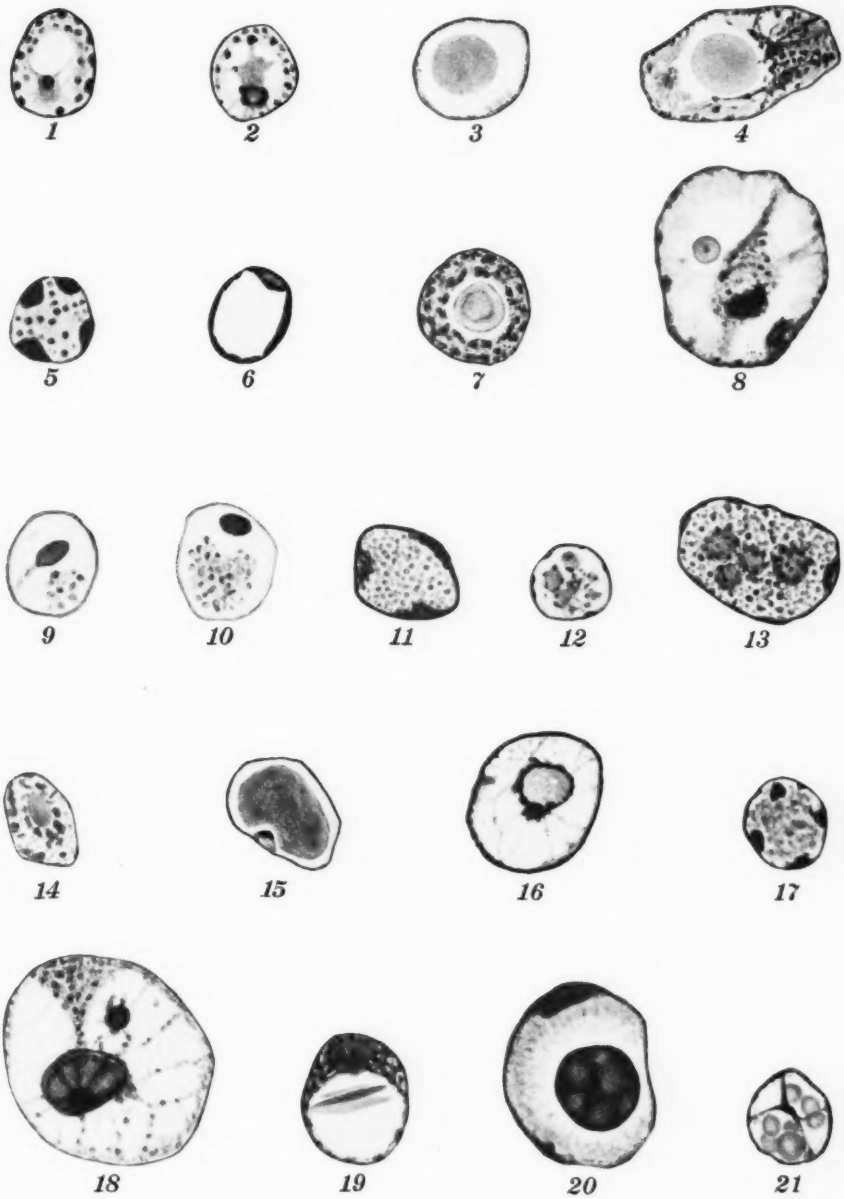
FIG. 17. *Black crested cockatoo.* Convoluted tubule. Type A inclusion with margination of basophilic nuclear chromatin.

FIG. 18. *Wonga Wonga pigeon.* Convoluted tubule. Nuclear hypertrophy.

FIG. 19. Same. Convoluted tubule. Nucleolar hypertrophy. Atypical crystalline acidophilic inclusion in a large clear area.

FIG. 20. *Marsh hawk.* Collecting tubule. Large type B inclusion staining also with basic dyes. Nuclear hypertrophy.

FIG. 21. *Ceropsis goose.* Convoluted tubule. Several types of B inclusions.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# LESIONS OF THE CORONARY ARTERIES AND THEIR BRANCHES IN RHEUMATIC FEVER *

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Karsner and Bayless'[1] very comprehensive analysis of the literature dealing with vascular disease occurring during the course of rheumatic fever has made it unnecessary to present a lengthy review of this subject. With the exception of the observations made by Bouillaud[2, 3] in 1835 and 1840, studies in this field were extremely vague until the latter part of the nineteenth century. This vagueness was due to the fact that the clinical and anatomical concepts concerning rheumatic fever were, for the most part, extremely ill-defined and that the scattered reports on vascular complications were generally based solely on clinical observations.

In spite of Bouillaud's reports, half a century elapsed before Krehl[4] laid the basis for our modern concept of the relation of rheumatic fever to coronary artery disease. In this amazingly complete report entitled "Beitrag zur Pathologie der Herzklappenfehler" Krehl foreshadowed much of the important recent work on the interstitial, often perivascular, lesions now known as Aschoff bodies, predicted the important relation of these lesions to the clinical conception of heart failure in rheumatic fever, and made the further contribution that in this disease arteriosclerotic changes occur in the larger vessels, with thickenings, infiltrations and intimal proliferations in the walls of smaller vessels.

The name of Romberg[5] must inevitably be linked with these earlier anatomical investigations on rheumatic fever. In 1894 this observer elaborated on Krehl's descriptions of coronary artery lesions, adding original observations on the occurrence of a diffuse hyaline thrombosis of the smaller arterioles and on the presence of a periarteritis involving a middle sized coronary artery. Since the beginning of the twentieth century many notable contributions have been made in this field, chiefly by Rabé,[6] Aschoff,[7] Barié,[8] Aschoff and Tawara,[9] Geipel,[10, 11] Coombs,[12, 13, 14] Gerhardt,[15] Takayasu,[16]

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Douglas,[17] Thalhimer and Rothschild,[18] Fahr,[19] Wätjen,[20] Wiesel,[21] Swift,[22] MacCallum,[23, 24] Pappenheimer and VonGlahn,[25] Shaw,[26] Talalajew,[27] Perry,[28] Klinge,[29-32] and Karsner and Bayless.[1] These workers confirmed the reports of Krehl and Romberg and added a number of new observations on a variety of lesions occurring in the coronary tree in this disease.* With very few exceptions these lesions were not considered specific of rheumatic fever. On the contrary, many of them were held to be similar to those found in other toxic and infectious diseases and in exanthemas (Martin,[33] Landouzy and Siredey,[34, 35] Huguenin,[36] Hanot,[37] Cowan,[38] Wiesel,[39] Wiesner [40]).

While the above mentioned contributions cover a variety of lesions which can be observed in the coronary arteries and their branches in the course of rheumatic fever, many of the reports are based on the observation of very few cases, at times on isolated instances. Furthermore, it appears that no systematic attempt has been made to study in detail all the lesions occurring in the active and inactive cases of rheumatic fever on a sufficiently large and representative material from which it might be possible to obtain statistical data on their incidence. The exhaustive study by Karsner and Bayless was undertaken from a different angle. These authors concerned themselves with the incidence of various progressive, retrogressive and inflammatory processes in the coronary tree as a whole, rather than with a description of the individual vascular lesions as they occur in different parts of the coronary system. Furthermore, their studies are confined to the incidence of these phenomena in active rheumatic cases and in normal controls. In this report we propose to classify and describe a number of distinctive vascular lesions found in active as well as inactive cases of rheumatic fever. Consideration will be given to the type of vessel involved and to the incidence of the lesions in various sites in the heart. Since some of these lesions are also found in normal control cases, statistical comparisons will be made with these.

The study is based on an examination of 100 hearts, 66 of which were from cases of acute rheumatic fever with Aschoff bodies in the myocardium and presenting the evidences of activity as outlined by Rothschild, Kugel and Gross [41] in a recent publication. The

* Since submitting this manuscript for publication a report has been published in which several additional vascular lesions of the coronary branches are described.
Fraser, A. D. Coronary endarteritis in acute rheumatism. *Arch. Dis. Childhood*, 1934, **9**, 267–276.

remaining 34 hearts were from inactive cases presenting the typical anatomical evidences of inactive rheumatic fever, *viz.* the characteristic valvular deformities with or without evidence of old auricular lesions, but without the presence histologically of swollen collagen, inflammatory cells, Aschoff bodies or fibrinous pericarditis. Fifty carefully studied normal * hearts, representing age periods from birth to the ninth decade, served as a baseline to establish deviations from the normal. The findings in this control series have been published elsewhere (Gross, Epstein and Kugel [42]). The hearts were generally fixed in 10 per cent neutral formol-saline.† For routine studies the standardized sections of Gross, Antopol and Sacks [43] were cut and stained with hematoxylin and eosin and with Weigert's elastic and Van Gieson's connective tissue stains. At times, Mallory's phosphotungstic acid hematoxylin, Weigert's fibrin method and Masson's trichrome stains were employed. The studies on the main coronary arteries were made on blocks removed from the left circumflex coronary artery 1 cm. from its ostium, from the left anterior descending branch 2 cm. from the ostium of the left circumflex coronary artery, and from the right circumflex coronary artery 1 cm. from its ostium.

In this report the vascular lesions of the main coronary arteries and their myocardial branches will be described and statistical data which concern only these vessels will be presented. Brief mention will also be made of the vascular lesions in the valves, and of the lesions in the roots of the pulmonary artery and aorta, together with the vascular lesions found in the pericardial sheaths surrounding these structures, but these will not be included in the statistical data. Studies in this field will be published in separate reports.

The lesions of the coronary artery tree found in active and inactive rheumatic fever can be divided into two categories. (*A*) *Evolutionary changes also found in normal control cases.* It will be shown that these normally occurring vascular lesions assume considerable significance in rheumatic fever because of their much more rapid and considerably earlier development in this disease. (*B*) *Lesions occurring either uncommonly, or never, in normal control cases.* It is

* In the selection of this material, diseases that were likely to implicate the coronary vessels were excluded, as were those hearts that showed obviously diseased coronary arteries on gross inspection.

† Solution of formaldehyde U. S. P. 10 parts, 1 per cent sodium chloride solution 90 parts. This solution is rendered neutral with a weak alkali.

not our purpose to lay claim to specificity for any of the lesions falling into this category. In order to do so it would be necessary to study extensively the coronary arteries and their branches in other inflammatory lesions of the heart and in febrile diseases. It is our impression, nevertheless, that many of the vascular diseases falling into this second category are so peculiar and so rarely met with in other diseases that their presence should lead to a strong suspicion of rheumatic fever in its active stages.

This report will be further subdivided into a description of the lesions due to rheumatic fever as they occur in the myocardial arteries * and into those found in the main coronary trunks. For purposes of clarity we shall first present seriatim a description of each lesion with a discussion of the incidence and sites of predilection. This will be followed by a discussion of these lesions considered from the point of view of their occurrence in active and quiescent rheumatic fever.

## Lesions of the Myocardial Arteries in Rheumatic Fever

### (*A*) *Evolutionary Changes also Found in Normal Control Cases*

#### 1. *Intimal Elastification*

By this term is meant a conspicuous increase in the intimal elastic membranes, irrespective of the cause of this increase. Thus, it may be the result of elastic-hyperplastic proliferation; it may follow the development of fibroblastic proliferation; or it may occur concomitantly with the evolution of the musculo-elastic layer. Elastification involving the intima of the myocardial arteries (Fig. 1) has been shown by us [42] to become fairly prominent during the third decade of life in normal control cases. At this age period it is seen with some regularity in the left posterior papillary muscle where the lesion eventually develops into its most advanced form. It occurs later, less consistently and less markedly, in the posterior wall of the left ventricle and in the interventricular septum. In these sites the lesion becomes prominent during the fifth decade. It occurs with great rarity in the auricular walls and the pulmonary conus. In the inactive rheumatic cases there does not seem to be a conspicuous increase in the incidence of this vessel lesion. In the active

* The coronary artery branches within the myocardium.

cases, however, the lesion occurs at times as early as during the fifth year of life and, in contrast to the normal controls, it may be seen in the pulmonary conus and the auricular myocardium. In the latter, even the arterioles may develop a thickening of the lamella elastica interna and become surrounded by a fairly dense elastic mantle (Fig. 2). This represents, therefore, a remarkable increase in the tempo of development of this normally occurring evolutionary vascular change. Beginning with the latter half of the first decade, intimal elastification can be found in almost every case of active rheumatic infection.

### 2. *Medial Elastification*

The same remarks apply to the vascular lesion that we have termed "medial elastification" (Fig. 3). In a previous report [42] we have shown that this lesion, which consists of the development of elastic membranes between the medial cells, does not become prominent until the middle of the third decade, when it is found with great regularity in the left posterior papillary muscle. As with the previously described vascular lesion, it does not appear with any degree of regularity in the posterior wall of the left ventricle and in the interventricular septum until the fifth decade of life. It is rarely found in the auricular myocardium or pulmonary conus. The appearance of this medial elastification in the active cases of rheumatic fever is of considerable interest, not only because of the extremely early age periods during which it may be found in this condition (4½ years), but also because of its widespread distribution and frequency of occurrence in the left posterior papillary muscle and interventricular septum in these early age periods. It is generally found in the posterior wall of the left ventricle from the beginning of the third decade on. It occurs rather infrequently and later in the auricles and pulmonary conus. As in the previously described lesion, there is no significant difference in the incidence of this lesion as between the inactive cases and the normal control series.

### 3. *Fibro-Elastification*

This is a term which we have applied to the fusion of the elastic-hyperplastic intima with a heavily elastified media. Simultaneously, there generally takes place a disappearance of smooth muscle with replacement by connective tissue. The resulting picture is one of

complete metamorphosis of the vessel in which the predominating features are fibrosis and elastification with or without the presence of irregular islands of smooth muscle tissue. The latter in turn may represent remains of the media or of the smooth muscle intimal layer (musculo-elastic layer). In its more marked form the topography of the vessel is markedly distorted (Fig. 4), the elastic membranes are irregularly thickened, frayed and ruptured, and present a very bizarre appearance. From the beginning of the third decade on, this type of lesion is found with great frequency in normal controls in the left posterior papillary muscle, and somewhat less regularly in the interventricular septum from the beginning of the fifth decade on. It occurs in exceptional instances in the posterior wall of the left ventricle in the later decades and is rare or absent in the other cardiac sites. It is found somewhat earlier but not frequently in inactive rheumatic cases in the left posterior papillary muscle, interventricular septum and the posterior wall of the left ventricle. It has been observed involving vessels of the interventricular septum at the age of 15 and has also been seen rather infrequently in the pulmonary conus. It has not been observed in the auricular myocardium in our inactive rheumatic material. In sharp contrast to this, however, is the appearance of this lesion in the active rheumatic cases where it has been seen as early as the age of 4½ years in the left posterior papillary muscle. It appears with greater regularity at about the age of 15 years. From the age of 20 years on it is seen quite prominently and almost invariably in the left posterior papillary muscle and in the interventricular septum. The lesion has also been seen in these active cases, though infrequently, in the pulmonary conus. It has not been observed in the auricular myocardium. It is the appearance of this very conspicuous, normally occurring lesion several decades earlier than is to be expected, which best exemplifies the influence of rheumatic fever in hastening normal evolutionary vascular changes.

### *4. Adventitial Fibrosis*

This lesion, which Wild [44] has recently emphasized in connection with rheumatic fever, consists of the development of a dense, wide, adventitial sheath. The vessel wall is seen surrounded by a conspicuous circular or oval zone of fibro-elastic tissue which may merge with neighboring scar tissue. Adventitial fibrosis is seen not in-

frequently in the active cases and very frequently in the inactive cases. It is generally difficult to distinguish it from unusually wide adventitial layers observed in control cases. However, in rheumatic fever, particularly in the inactive stages, it is found in considerably earlier age periods where it may be quite extensive. The sites of predilection are the left posterior papillary muscle and the interventricular septum. It occurs with lesser frequency in the posterior wall of the left ventricle.

### (*B*) *Lesions Occurring either Uncommonly or Never in Normal Control Cases*

#### *5. Medial Glassy Hypertrophy*

In approximately half of the active cases of rheumatic fever, one encounters in the smaller myocardial arteries and in the arterioles, practically throughout the heart, a swelling of the smooth muscle cells which take on a glassy appearance and present rather indistinct outlines of the cell walls (Fig. 5). The nuclei tend to occur in clusters and become somewhat rounded. The nuclear membrane and chromatin particles are quite sharp and distinct. This lesion is extremely uncommon in the inactive cases. It is rare in the control cases but has been noted repeatedly in other inflammatory diseases in the myocardium and in febrile conditions. It is obviously nonspecific and is an evidence of an irritative process. There does not appear to be any special site of predilection for this lesion.

#### *6. Medial Hypertrophy*

This is an extremely uncommon lesion in normal controls where a hypertension, past or present, can safely be ruled out. It is represented by very obvious thickening of the vessel wall, due to an increase in the number and size of the smooth muscle cells. The lesion occurs very rarely in the inactive cases. It is one of the most frequent findings in the active cases and is seen particularly prominently in the retro-aortic myo-epicardial auricular wedge.* It occurs less frequently in the posterior wall of the left ventricle and in the interventricular septum. Hypertrophied vessels of this type are also frequently found near the septum fibrosum, in the pericardial tissue

* A. M. V. section of the standardized blocks. [43]

close to the auriculoventricular groove, in thickened rheumatic valves and in the subaortic angle. Of interest is the fact that in the active cases this vascular lesion occurs with almost the same frequency in young (17 months) and old.

### 7. *Intimal Fibrosis*

One of the most frequently occurring coronary vascular lesions in rheumatic fever, confined largely to the active cases, is a thickening of the intima due to fibroblastic proliferation (Fig. 6). While intimal fibro-elastic changes are frequently encountered in the normal control series, particularly in the later age periods, the development of a clean-cut concentric or eccentric widening of the intimal layer by a zone of non-elastified connective tissue has not been found in these controls. In active rheumatic infection this lesion is distributed, though somewhat irregularly, throughout the myocardium. Its site of predilection is the left posterior papillary muscle, where it is found quite regularly, even in the earliest age periods. The lesion apparently occurs quite rapidly in active rheumatic fever. As a consequence, it may be observed in those vessels that have not as yet developed elastic-hyperplastic changes. Undoubtedly this fibroblastic layer eventually becomes elastified. Indeed, it seems reasonable to assume that intimal fibrosis is not infrequently the precursor of intimal elastification in cases of rheumatic infection. Since it occurs even in the youngest cases it may account for the early development of intimal elastic changes in these cases. The fibrosis is not infrequently eccentric and may lead to marked narrowing of the vessel. Superimposed on this fibrotic intima one may at times observe a swelling and proliferation of the endothelial cells.

Intimal fibrosis may be superimposed on intimal elastification. In such cases there develops internally to the innermost intimal elastic lamella a distinct zone of varying width consisting of collagen and connective tissue cells (Fig. 7). The layer is in turn lined by endothelium. This rather sharp lamination of the intima by elastic and fibrotic zones suggests that they are the results of older and more recent rheumatic bouts.

### *8. Giant Medial Hypertrophy with Metallaxis*

This lesion is represented by a conspicuously and unusually florid hypertrophy of the media (Fig. 8). The cells are generally somewhat irregularly arranged (metallaxis) and may or may not present discontinuous elastic membranes between them when these are present. The chief differences between what we have termed "giant medial hypertrophy with metallaxis" and the lesion described under the term "medial hypertrophy" lie in the considerably greater extent of the hypertrophy, the irregularity in the planes of the muscle fibers, the frequently irregular distribution of the elastic membranes when present, the occasionally vague and bizarre appearance of the inner aspect of the adventitial layers, and frequently in the presence of edematous spaces between the medial smooth muscle cells. A lesion somewhat resembling giant medial hypertrophy was seen in the left posterior papillary muscle and in the interventricular septum in only 2 out of the 50 normal control cases at the ages of 23 and 45 years respectively. In the inactive rheumatic cases it was not found. On the other hand, the lesion was observed in 8 of the 66 active cases, generally in the retro-aortic myo-epicardial auricular wedge, where it has been found as early as at the age of 3½ years. It is found with greater frequency in the pericardial sheath surrounding the root of the pulmonary artery but, as has been indicated, in this report the vessels in this site will be considered separately from the myocardial arteries proper. Because of the infrequency of this vessel lesion in the control group, it seems best to include it in the second large group of our classification.

### *9. Medial Edema*

Besides the "giant medial hypertrophy with metallaxis," several other vascular lesions, especially the arteritides, and particularly those associated with necrotization (*vide infra*), showed a conspicuous edema of the media (Figs. 11, 16, 23, 24, 25, 26, 28). If one bears in mind the artifacts created by tissue fixation, genuine edema of the media is relatively infrequently encountered. It occurs somewhat more often in the main coronary arteries. This will be discussed further. Incidentally, a cross-section of the intimal musculo-elastic hyperplastic lesion gives the impression of the "état reticulaire" of the media quoted by Karsner and Bayless. Longitudinal sections

of such vessels stained for elastic tissue disclose that the reticular appearance is due to intimal longitudinal smooth muscle cells which may be hypertrophied, somewhat swollen and pale staining.

### 10. *Arteritis (Exudative and Necrotizing)*

Under the term "arteritis" there is considered definite inflammatory infiltration of the vessel wall with or without necrosis, and without the distinctive histological features that characterize the special forms to be described. The lesions vary from a relatively mild infiltration of one of the main layers of the artery with lymphocytes and the presence of edema, to an active destructive infiltration with polymorphonuclear leukocytes (Fig. 9), plasma cells and, at times, basophilic cells characteristic of the Aschoff body. As noted by VonGlahn and Pappenheimer,[45] many of the wandering cells are oriented in the direction of the lumen. Fibrinoid swelling of the collagen may be present. The lesion may be so extensive and destructive and the media may undergo such conspicuous necrosis that a picture is produced which is indistinguishable from the necrotizing arteritis of so-called polyarteritis nodosa. Together with these inflammatory and destructive phenomena there may be seen irregular proliferations of the intimal endothelium or of the mesenchymal tissue lying beneath the endothelium. These cells may be arranged in palisade form and the internal and external elastic membranes may assume a glassy swollen appearance or become ruptured and disappear. Thrombi have been observed within the lumens of such actively inflamed vessels.

There does not appear to be any advantage in subdividing the various grades of exudative and necrotizing arteritis occurring in rheumatic fever. While arteritis of this type was never found in the inactive cases, it was observed in 11 of the 66 active cases examined, where it occurred chiefly in the interventricular septum with about an equal distribution in the other cardiac sites. In 4 of these cases (reported in detail by Friedberg and Gross[46]), the lesions were so extensive and associated with such definite involvement of the vessels elsewhere in the body that the cases were considered polyarteritis nodosa associated with rheumatic fever.

Apart from these 11 cases presenting various forms of exudative and necrotizing arteritis in the myocardial arteries, 8 additional

cases displayed the special forms of arteritis to be described (*vide infra*). Of this total of 19 cases, 8 also presented inflammatory phenomena in the main coronary arteries. In 2 additional cases the inflammatory lesions were confined to the main coronary arteries. In 1 additional case a fibrinoid necrosis of the coronary vein was noted, and in 1 other a verrucous endophlebitis associated with inflammatory lesions of the myocardial arteries. These figures on the incidence of the lesions in the veins are undoubtedly too low, since no systematic study was made of the venous system. Disregarding the latter, therefore, it would appear that 33 per cent (22 out of 66 cases) of the active cases presented some form of arteritis in the arterial tree of the heart. It should be noted that this figure is also exclusive of the inflammatory lesions in the pulmonary artery and aorta.

### *11. Subendothelial Hemorrhagic Arteritis*

This corresponds to one of the vascular lesions described by Von Glahn and Pappenheimer [45] as occurring in a variety of tissues including the aortic valve. It consists essentially of a hemorrhage beneath an otherwise intact, sometimes swollen endothelium, raising it away from the vessel wall (Fig. 10). The lumen may contain a hyaline thrombus and the wall show moderate infiltration with inflammatory cells. This lesion was not encountered in the normal controls or in the inactive cases. It was found in 4 active cases (in 2 it occurred in the retro-aortic myo-epicardial auricular wedge) and may possibly represent a specific lesion of rheumatic fever.

### *12. Net-Like Fibrinous Thrombosis Affecting Small Myocardial Arteries*

This is another vascular lesion described by the above mentioned authors as occurring in the small peripheral arterioles and capillaries, and considered by them specific of rheumatic fever. As observed by them in a variety of organs, it is "characterized by the exudation of fibrin into and about the vessel, by destructive changes in the cellular components of the vessel wall, by a distinctive cellular reaction in the adjacent tissue and by the absence of thrombosis. These acute lesions are followed by organization with or without formation of new collateral channels within the thickened intima and occasionally within the muscular layer." A somewhat similar

lesion was noted by them about a small capillary in the heart. The vessel over a small area was surrounded by a mass of fibrin which infiltrated the surrounding tissue. At the margin of the fibrin there were many Aschoff cells and a few polymorphonuclear leukocytes. The lumen was not occluded by thrombus and the endothelium was intact.

We observed this lesion in the retro-aortic myo-epicardial wedge of the right auricle in 1 case. Here, the inflammatory phenomena in the wall of the vessel and within the periadventitial tissue were limited in their extent. The most characteristic feature was a net-like formation of fibrin within the lumen of the vessel (Fig. 11), thus differing from the typical blood platelet thrombus. As noted by VonGlahn and Pappenheimer, in the organization of this lesion the fibrin network is apparently displaced by connective tissue with the formation of a cavernous type of canalization.

### *13. Endarteritis Verrucosa*

In 1924 and 1926, Holsti [47, 48] described peculiar proliferative lesions occurring as finger-like processes within the vessel lumens of tonsils and the gastro-intestinal tract in "arthro-nephro-cardiopathies." Under the title "arteriitis verrucosa," Holsti [49] described the mechanism of their formation as being either primary, representing a vascular lesion *sui generis*, or secondary to such vascular changes as lead to a thrombosis. The term "endarteritis verrucosa," as employed by us, refers to the formation of typical endarterial verrucae probably identical with those seen on active rheumatic valves (Fig. 12). While the material available for study of this lesion was too limited to permit an exhaustive investigation of the mechanism of its formation, it would appear that a fibrinoid necrosis of the intimal layers of the vessel with fusion of the various histological elements may be followed by, or associated with, deposition of blood platelet thrombi. This eventually leads to organization. If the original verrucous lesion is large and polypoid, the organized plug is eventually represented by a finger-like connective tissue process within the lumen of the vessel — a lesion which we shall refer to as "endarteritis polyposa." The organized verrucous plug may be attached to the vessel wall at several points, producing a canalization of the lumen. Thus, it will be seen that this lesion oc-

cupies an intermediate position between necrotizing arteritis on the one hand and intravascular thrombosis on the other. Typical endarteritis verrucosa was found in the myocardial arteries only in 2 active cases, where the individuals were 4½ and 10 years old respectively. There was no special site of predilection. In addition, it was seen in the left anterior descending coronary branch in 1 case.

### *14. Granular Plugged Vessels*

This lesion bears a superficial resemblance to the early stages of endarteritis verrucosa and polyposa. In its typical form it consists of a spherical, oval or lobated, finely granular mass which partially or completely occludes the lumen of the vessel (Fig. 13). It is generally covered by a somewhat swollen endothelium and frequently contains several nuclear ghosts within its substance. It would appear that the lesion is produced by proliferation of vascular endothelium with swelling and granular transformation of the protoplasm, fusion of the cells and degeneration of the nuclei, a process described as occurring in atypical verrucous endocarditis (Gross[50]). In the healing of these granular masses organization takes place with replacement by connective tissue. The end result may therefore be a parietally situated fibrous plug within the lumen of the vessel, a centrally situated polypoid mass, in which stage it is classified as endarteritis polyposa, or a canalization of the lumen. Granular plugging of the myocardial arteries was observed in only 3 active cases, where the individuals were 15, 25 and 38 years respectively. The site of predilection appeared to be the interventricular septum. One of the cases (age 25 years) showed, in addition, an extensive and almost completely occluding granular plugging of the left circumflex coronary artery (Fig. 28).

### *15. Thrombosis*

Thrombosis of myocardial arteries directly attributable to rheumatic injury of the vessel rather than to a primary or secondary sclerotic vascular damage was seen in only 4 active cases. Three of these (age 7½, 10 and 30 years) were associated with a marked necrotizing arteritis (polyarteritis nodosa). In one of these (age 7½ years), there was also present a thrombosis of the left circumflex coronary artery. In the fourth case (age 17 months), also asso-

ciated with an arteritis (but not of the necrotizing type), large branches of the left circumflex coronary artery showed the presence of occluding typical blood platelet thrombi and there was present extensive myocardial infarction. This case also presented a thrombosis of the main left circumflex coronary trunk (Fig. 27). While on this subject, it is pertinent to mention that red blood cells and sometimes fibrin plugs are not infrequently encountered occupying the lumens of various small coronary vessels in active rheumatic fever. While it is at times tempting to call these thrombi, we have reserved this designation for the typical layered blood platelet intravascular collections which definitely are of *intra vitam* formation and which are partially or completely occluding and generally associated with myocardial infarction of various degrees. As in the case of endarteritis verrucosa, organization of typical thrombi results either in parietally or centrally situated, partially or completely occluding connective tissue plugs, or, polypoid masses may be formed within the lumen of the vessel, or finally, canalization may take place.

### *16. Canalized Vessels*

It was already mentioned that the healed lesions following net-like thrombosis, endarteritis verrucosa, granular plugging of vessels and thrombosis may be represented by a canalization of the vessel lumen (Figs. 13, 14). As a consequence, these lesions have been found only in the active cases and occur somewhat less frequently than the corresponding lesions which produce them. These canalized vascular lesions have also been observed in atypical verrucous endocarditis (Gross[50]).

### *17. Endarteritis Polyposa*

As has already been indicated, this term is applied to the end stages of a variety of lesions. It consists of a polypoid or finger-like plug of organized or organizing connective tissue which is situated within the lumen of a vessel and is separated from the vessel wall throughout its greater extent (Fig. 15). It may result from endarteritis verrucosa, granular plugging or genuine thrombosis. It was observed only in 3 active cases where the individuals were 17 months, 10 years and 38 years respectively.

### *18. Aschoff Bodies Associated with Blood Vessels*

The frequent, but by no means invariable, proximity of Aschoff bodies to blood vessels has been repeatedly emphasized. These may assume a very intimate relation to the vessel wall. In rare instances other observers have noted an apparent compression of the vessel lumen by this lesion. Karsner and Bayless believe that this compression has little if any influence on the circulation within. Rather infrequently, irregular basophilic cells, somewhat resembling those of the Aschoff body, are found within the media. It is very likely that in many cases these represent merely hypertrophied and somewhat altered medial smooth muscle cells. As already mentioned, eventual transformation of the Aschoff body into connective tissue scar undoubtedly accounts for most of the adventitial scarring.

### *19. Intimal Musculo-Elastic Hyperplastic Lesion*

While the development of smooth muscle cells within the elastic-hyperplastic layers of the intima is a normal evolutionary process, the cells are relatively few in number, seldom attain more than one or two layers in thickness and are generally somewhat irregularly distributed. Moreover, the elastic-hyperplastic changes are not infrequently more conspicuous than the smooth muscle elements. In distinct contrast to this is the "intimal musculo-elastic hyperplastic lesion." This is one of the most characteristic vessel lesions seen in rheumatic fever and consists of the development of numerous layers of longitudinal smooth muscle cells which lie internally to the lamella elastica interna and are covered by a generally swollen, sometimes raised endothelium (Fig. 16). These smooth muscle cells frequently show mantles of elastic tissue which, on cross-section, present a honeycombed appearance. This intimal musculo-elastic zone is generally concentrically placed, may be eccentric (Fig. 17) and is often so extensive as to occlude almost completely the vessel wall. In some instances, the smooth muscle cells are very large and pale staining.

As with other intimal vascular changes in rheumatic infection, the end state of the intimal musculo-elastic hyperplastic lesion appears to be an elastification (Fig. 18). This consists of a conspicuous increase of elastic tissue which, together with connective tissue, even-

tually replaces the smooth muscle elements. At times, the intima contains several, irregular, laminated layers of musculo-elastic tissue separated by heavier elastic membranes (Fig. 19). Such lesions suggest the possibility that these layers represent repeated attacks of rheumatic fever.

The development of a somewhat similar musculo-elastic hyperplastic layer, but in considerably abbreviated form with the smooth muscle cells rather irregularly arranged, has been seen in one of our normal hearts at the age of 47, and in one at the age of 65 years. Both occurred in the posterior wall of the left ventricle. In one other case, aged 9 months, a vessel of this type was seen in the pericardial sheath surrounding the pulmonary artery. In the inactive rheumatic cases the lesion was seen once in the interventricular septum in a patient aged 26, once in the retro-aortic myo-epicardial auricular wedge in a patient aged 68, and once in the aortic pericardial mantle in a patient aged 30 years. In the active rheumatic group it was seen in approximately half of the cases. Its distribution was chiefly in the retro-aortic myo-epicardial auricular wedge and in the region of the septum fibrosum, including the posterior portion of the interauricular septum. The next most frequently involved site was the pericardial sheath surrounding the pulmonary artery. The lesion was least frequently seen in the posterior wall of the left ventricle, in the left posterior papillary muscle, pulmonary conus and interventricular septum. Apart from these myocardial sites this lesion is found in the subaortic angle and in thickened rheumatic valves, where it occurs with considerable frequency.

The occurrence of these intimal musculo-elastic lesions in greater numbers and in exaggerated form is so highly characteristic that, with the possible exception of syphilis, in which a somewhat similar lesion has occasionally been observed, their presence is highly suggestive of active rheumatic involvement. This is particularly true when the intimal musculo-elastic hyperplastic lesions, together with others which have been described above, are found in the left auricular myo-epicardial wedge (Fig. 20) and in the region of the septum fibrosum, including the conduction system.

### Lesions of the Pulmonary Artery and Aorta

Besides the above mentioned findings, various inflammatory lesions, vascularization and scarring, occur with remarkable regu-

larity in the pulmonary artery and aorta in both the active and inactive cases. This will be taken up in a separate report. It is noteworthy, however, that in the pericardial sheath behind these vessels one very frequently encounters medial hypertrophy, giant medial hypertrophy with metallaxis and intimal musculo-elastic hyperplastic lesions. These are seen with conspicuous frequency in the active cases and form a characteristic part of the picture presented by blood vessels in rheumatic fever.

In presenting the above mentioned findings we have deliberately avoided including in our statistical data the vessel lesions found within the valves, subaortic angle and subendocardium. These are generally of the medial hypertrophied, giant medial hypertrophied, intimal musculo-elastic hyperplastic and thickened granulation tissue capillary types. By themselves, they form conspicuous vascular lesions, but inasmuch as they represent, in our opinion, the end stages of newly formed vessels, we have not considered it justifiable to include them in the group of vascular lesions affecting the preexisting coronary arteries and their branches.

## Lesions in the Main Coronary Arteries Due to Rheumatic Fever

### *Inactive Cases*

We have already shown [42] that in normal control cases all three layers of the coronary arteries undergo a series of evolutionary changes which present considerable variations, not only during the various age periods but also in individual cases. It appears that the rate of development of these changes may vary markedly from individual to individual. It is, as a consequence, extremely difficult to determine whether the main coronary arteries display these changes in a given case in a more marked form and earlier, because of the rheumatic involvement. It appears, nevertheless, that even in inactive rheumatic cases there is a tendency toward an earlier development of heavy intimal elastic-hyperplastic and fibrotic layers, and for the appearance of heavier elastification and scarring of the media.

The elastic tissue in the media of normal coronary arteries appears to increase during the early age periods and decrease thereafter. Furthermore, while there is a certain amount of cross-weaving

of the elastic fibers, they run as a whole parallel to the main axis of the lumen. In the inactive rheumatic cases the elastic tissue shows a consistent increase in amount from the early age periods on, and the direction of the fibers not infrequently shows considerable distortion and irregularity, appearing as scattered, heavily elastified patches (Fig. 21). This condition is not to be confused with the patchy medial elastification appearing under sclerotic intimal plaques. Nor is it to be confused with the irregular reticular elastified areas found not infrequently in the media of normal coronary arteries and associated with the presence in the media of what we have termed "intermediary layers." [42] One of the illustrations in the article by Karsner and Bayless appears to represent such a normally occurring vascular architectural variant.

Discontinuities in the medial elastic membranes are not infrequent, particularly after the third decade of life. Before concluding that there is present rupture of these membranes in a given case, the normally occurring discontinuities should be borne in mind, and only when there is present a very obvious disruption of these membranes in areas which do not contain the "intermediary layers," should this diagnosis be made. Rupture of the medial elastic membranes is relatively infrequent in the inactive cases. When it occurs it is generally associated with scarring.

Similar remarks apply to scarring of the media. This can be considered as of rheumatic origin only in obviously scarred areas (larger and more irregular than the normally occurring fibrotic mosaic), when they are focal in their distribution and not situated directly beneath an arteriosclerotic plaque with lipoid and calcific deposition (Fig. 22). Considered along these lines, moderate scarring and elastification of the media occur either in the left circumflex coronary artery, right circumflex coronary artery, or the left anterior descending coronary artery in approximately one-third of the inactive cases. It was marked in four of these. There did not seem to be a predilection for any one of these three main vessels.

We have been discouraged in our attempts to evaluate the changes in the amount of chromotropic substance to be found in the coronary arteries. It appeared to us that the technical factors involved, and the uncertainty in estimating these changes, rendered such a study too much open to criticism. It should be mentioned, however, that whereas Karsner and Bayless were unable to demonstrate this sub-

stance in the coronary vessels of control cases, they observed it frequently in their active rheumatic material. With regard to the presence of medial edema it may be said that its occurrence in sites not in the immediate vicinity of sclerotic intimal plaques was rather infrequent and too ill-defined to permit of reasonably accurate appraisal.

It is as well to mention here that we have been rather strict in our definition of "fibrinoid change." Karsner and Bayless define this as "an intensely acidophilic substance, arranged in fibrillar fashion, sometimes with beading at intersections." According to this definition these authors observed fibrinoid change in many of their control cases. However, unless the tissue showed distinct swelling with loss of outlines and unless the tinctorial alterations were very marked, we have not used the term "fibrinoid change." With this somewhat stricter definition in mind, we have not been able to demonstrate these changes either in the normal control cases or in the inactive cases.

### *Active Cases*

While the above mentioned changes are the only ones that we have been able to observe in the inactive cases, and we repeat that one can offer little more than a suggestion of this increased tempo of vascular retrogression, these phenomena seem to occur more frequently and to appear much earlier in the active cases. Noteworthy differences from the former are the greater incidence and extent of edema in the media, even in the absence of an arteritis (Fig. 23); the relative paucity of elastic fibers in the thickened intima, particularly in the earlier age periods, and the presence in a fair number of cases of what we have termed "reduplicated intimal layers." This consists in the early stages of a generally loose, somewhat myxomatous tissue, covered by endothelium and situated on the innermost aspect of the intima (Fig. 24). This layer is seen to be distinctly superimposed on the intima proper, and in later stages apparently becomes elastified. When present, this reduplicated intimal layer may possibly represent one of the results of an attack of rheumatic fever.

The most obvious and distinctive lesions of the main coronary arteries which are found only in the active cases are the exudative, necrotizing and other peculiar types of arteritis similar to those de-

scribed as occurring in the myocardial arteries. These lesions occurred in 10 of the 66 cases (15 per cent). The exudative lesions consist of inflammatory involvement of varying grades of intensity, generally affecting the media. In some forms there may be seen marked edema of the media (Fig. 24) with swelling of the smooth muscle fibers, rounding of the nuclei with prominence of the chromatin, and the presence of inflammatory cells. In other forms of exudative arteritis the predominating cell type is the polymorphonuclear leukocyte, sometimes the lymphocyte. These cells occur either diffusely, sometimes more abundantly seen toward the intimal aspect of the vessel, or are localized in one arc of the circumference of the vessel. Ameboid streamers of polymorphonuclear leukocytes and monocytes are almost invariably seen. The latter sometimes contain fairly large nuclei with rather abundant basophilic cytoplasm. Eosinophiles and mast cells are seen less frequently and irregular basophilic cells, somewhat resembling those found in Aschoff bodies, are rare.

Together with the inflammatory cell accumulations, there was sometimes found a fibrinoid swelling of the collagen. Rupture and dissolution of the elastic membranes occurred only in the very active cases (Fig. 25), particularly in those associated with polyarteritis nodosa (Fig. 26). Pictures simulating rupture of the elastic membranes were occasionally found. Their significance has already been discussed under the findings of the main coronary arteries in the inactive cases.

Both in the active and inactive cases, inflammatory cells, generally lymphocytes, were not infrequently met with in the adventitial and periadventitial layers. In the active cases this was a more frequent occurrence, where also polymorphonuclear leukocytes, monocytes and, at times, Aschoff bodies were also present. It is of interest that these adventitial and periadventitial infiltrations occur even in the absence of macroscopic pericarditis. However, even in the inactive cases, microscopic pericarditis, *i.e.* diffuse, rather mild lymphocytic infiltrations of the visceral pericardium, occurs with great frequency.

While all three main coronary trunks, *viz.* the right circumflex, left circumflex and left anterior descending, were seen involved in some of these cases, it appears that of the three the lesions were found with about the same frequency in the left circumflex and

left anterior descending trunks, and least often in the right circumflex coronary artery. Apart from the above mentioned forms of exudative and necrotizing arteritis (seen in 6 cases), proliferation of the intimal endothelial and subendothelial cells with formation of palisades was found in the left circumflex coronary artery in 1 case (age 6 years), occluding thrombosis of the left circumflex coronary artery (Fig. 27) with myocardial infarction in 2 cases (age 17½ months and 7½ years), verrucous endarteritis involving the left anterior descending branch in 1 case (age 9 years), and a granular plugged lesion (Fig. 28) almost completely obliterating the left circumflex coronary artery in 1 case (age 25 years). Of great importance is the fact that, with the exception of the last mentioned lesion, all the inflammatory phenomena found in the main coronary vessels in active rheumatic fever occurred during the first 15 years of life. This affords additional evidence of the extraordinarily dramatic course taken by this disease in the young, a point of perhaps some immunological significance.

Returning to a consideration of the changes in the main coronary arteries in active cases, which are similar to those found in inactive, as well as in normal control cases, one notes, as mentioned before, the development of increased medial elastification (as early as 6½ years) and a much earlier and considerably advanced tempo in the formation of intimal hyperplasia. An illustration of the latter is a case where the individual was 15 years of age, which showed an intimal thickening approximately four times the size of the media in the right circumflex coronary artery. This process normally appears during the fourth decade of life. In another case (age 29 years) the left circumflex coronary artery showed an intima ten times the thickness of the media, whereas it is generally twice the thickness of the media at this age period. A not inconsiderable number of cases similar to these mentioned, emphasizes the fact that besides active inflammatory and destructive phenomena, rheumatic fever induces in the walls of the main coronary arteries a series of precocious evolutionary metamorphoses which cannot be differentiated from those occurring normally as the result of age.

## Discussion

Consideration of the lesions described in this report makes it evident that both from the point of view of their frequency and of their

extent, the coronary arteries and their branches in the heart show very marked damage due to rheumatic fever. This damage is very vivid and impressive in the active cases. Indeed, it may be so extensive that it would be difficult if not hazardous to venture an opinion as to whether the vascular or primary myocardial injury is the more significant with regard to the life of the patient.

In the inactive cases the lesions do not appear to be essentially dissimilar from the normally occurring evolutionary age period changes. As has been indicated, however, a significant difference lies in their somewhat more rapid development. Since these changes, both in the myocardial arteries as well as in the main coronary branches, merge imperceptibly with what is considered arteriosclerosis, it would appear that in the majority of instances the entire vascular damage and its consequences in these inactive cases may be attributed to an earlier fibro-elastification of the myocardial arteries in rather important sites of the heart (where ischemia is more likely to occur) as well as to the earlier appearance of arteriosclerosis in the main coronary trunks. This point of view has been recently stressed by Zeek[51] and by Karsner and Bayless.[1]

It has already been mentioned in a previous publication [42] that fibro-elastification of vessels, particularly in the interventricular septum and posterior wall of the left ventricle, may be of significance, inasmuch as these vessels become transformed into more or less passive rigid tubes, little if any subject to vasomotor control. If this process should take place so early in life and so rapidly that there has been very little opportunity for the development of compensatory anastomotic channels, the consequences are likely to be those following myocardial ischemia. How great a rôle, if any, this mechanism, apart from lesions of the main trunks, may play in accounting for some of the symptoms of angina pectoris occurring in a number of these inactive rheumatic cases, is a matter for conjecture.

The findings in the main coronary arteries in the inactive cases are, however, by no means as strikingly clear-cut as are those in the active cases. Here, besides the considerably earlier development of intimal hyperplasia (often of a fibrotic type) and medial elastification and scarring, there also occurred in a significant incidence (15 per cent) a variety of arteritides which are represented by various grades of exudative and necrotizing inflammation, by thrombosis,

as well as by certain peculiar vascular and intravascular lesions, *viz.* edema, palisade formation, endarteritis verrucosa and granular thrombotic lesions. Together with these lesions in the main coronary trunks, the smaller vessels distributed throughout the myocardium presented similar changes in 19 cases. The total incidence of the various types of arteritis occurring in either the main coronary trunks, the smaller myocardial vessels or both, was 33 per cent. The incidence of these lesions in various cardiac sites in order of their frequency was as follows: the interventricular septum, the retro-aortic myo-epicardial wedge, particularly in the region of the septum fibrosum, the posterior wall of the left ventricle, the left posterior papillary muscle and the pulmonary conus.

Furthermore, in these active cases the myocardial vessels displayed a number of normally occurring evolutionary changes more frequently, more extensively and considerably earlier than those found in normal control cases. There was also present a series of degenerative, productive and proliferative changes which are either uncommonly or never seen in normal cases. The clinical implications of such widespread vascular damage are obvious.

There remains to be discussed the possible relation of the lesions occurring in active cases to those found in the inactive cases. An examination of the sites of predilection of the lesions occurring in the active cases discloses that some of the non-arteritic lesions closely parallel the incidence of the lesions found in the inactive cases. This suggests a sequential relationship. The observation that other non-arteritic lesions occur almost exclusively in the active cases and the fact that these were on the whole from considerably younger age periods than the group comprising the inactive cases, suggests an eventual transformation of these non-arteritic lesions into the types seen in the inactive cases. This is probably brought about by a process of elastification. The possible relationship which these events may bear on an earlier development of an arteriosclerotic process has already been discussed. On the other hand, the arteritic lesions show little if any parallelism in their sites of predilection with the lesions found in the inactive cases. One must conclude either that they may heal with little discernible residua or the patients affected with such destructive lesions are less likely to reach the protracted inactive stages of the disease.

From the anatomical point of view the realization that there occur

in the smaller branches of the coronary arteries many different types of vascular lesions, only four of which are similar to those found as normal evolutionary changes, that a number of these are active and destructive, and that some are of such unusual appearance that they possibly represent specific entities, brings to the pathologist additional evidence on which to build up the curiously complex picture which constitutes the anatomical lesions of rheumatic fever. A consideration of the variety and wide distribution of these lesions affords additional support to the belief that the heart is the most extensively involved organ in the body in this disease. It appears further that the various rheumatic vascular affections of the heart produce their damage during the active as well as the inactive stages. During the active states the acute inflammatory and destructive lesions occur. In the quiescent periods the heart is handicapped by the considerably advanced age period changes which occur in the coronary tree.

## Summary and Conclusions

A description has been presented of the vascular lesions in the main coronary arteries and their branches as they occur in active and inactive rheumatic fever, together with a statistical indication of the frequency of their occurrence, sites of predilection and comparison with the findings in normal control cases. The lesions in the myocardial branches have been classified under a number of different headings. Four of these are similar to the evolutionary age period changes found in normal control cases. Several of the remaining lesions are so peculiar in their structure as to suggest the possibility that they may be specific of rheumatic fever. This conclusion, however, cannot be accepted as final without an extensive search for similar lesions in other affections of the myocardium.

A discussion is given of the mechanism concerned in the development of these lesions, of their possible relation to the development of the arteriosclerotic process and of their clinical significance.

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## DESCRIPTION OF PLATES

### PLATE 32

FIG. 1. Myocardial artery in posterior papillary muscle showing intimal elastification. Age 38 years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

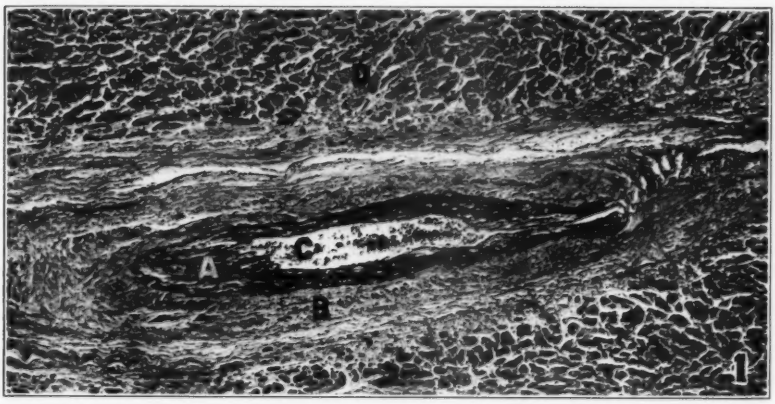
A = elastified intima; B = media; C = lumen of vessel containing red blood cells; D = myocardium.

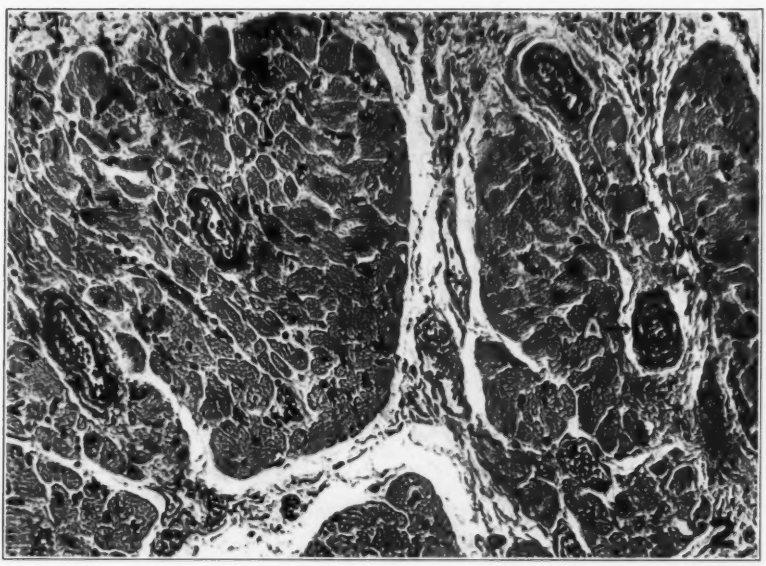
FIG. 2. Myocardial arterioles in left auricle showing thickening of lamella elastica interna and formation of external elastic limiting membrane. Age 13 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

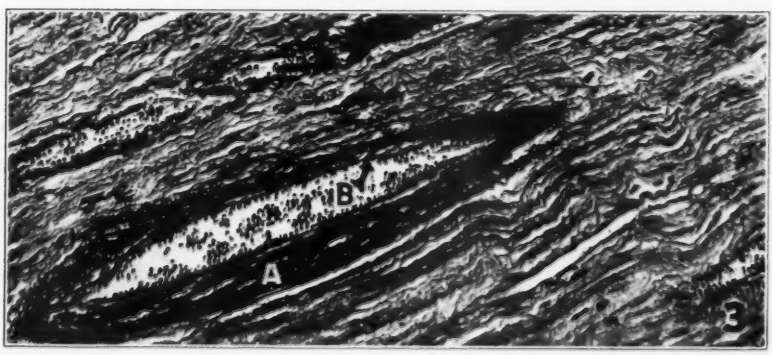
A = typical arteriole showing heavy internal and external limiting elastic membranes.

FIG. 3. Myocardial artery in posterior papillary muscle showing medial elastification. Age 38 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = enormous development of elastic fibers between smooth muscle cells of media; B = lamella elastica interna.




Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

PLATE 33

FIG. 4. Myocardial artery in posterior papillary muscle showing fibro-elastification. Age 38 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

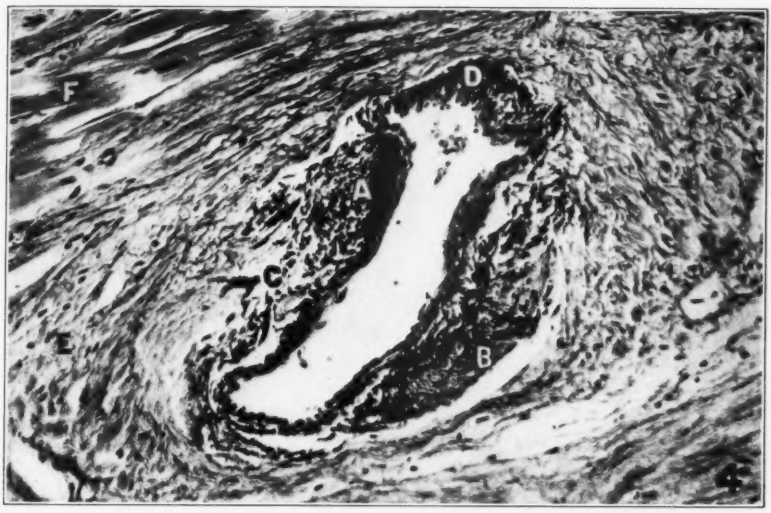
A = marked distortion, fraying and rupture of elastic membranes of fused media and intima; B = disoriented, medial smooth muscle cells; C = irregular scarred area of media; D = fused elastified intima and media with complete disappearance of smooth muscle cells; E = adventitia; F = myocardium.

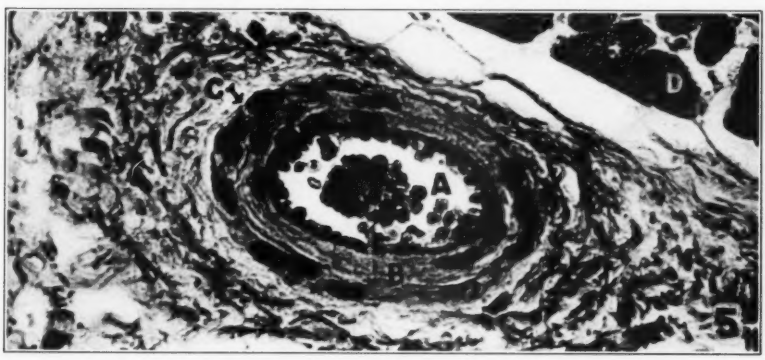
FIG. 5. Small myocardial artery in posterior papillary muscle showing glassy hypertrophy of media. Age 14 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

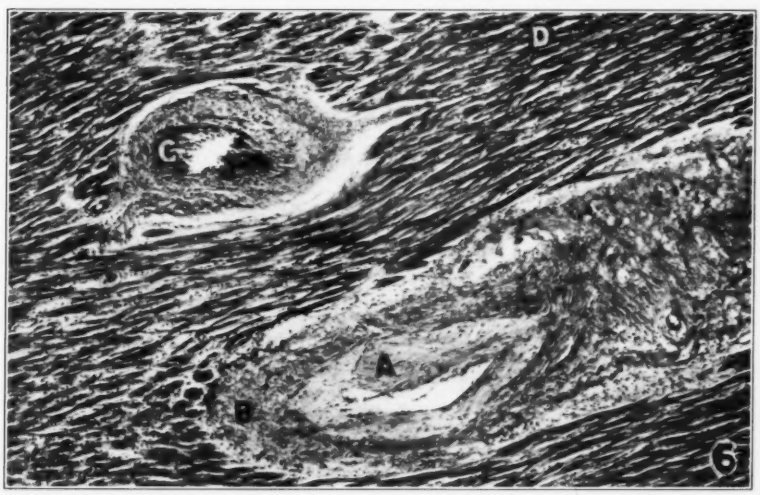
A = lumen of vessel containing red blood cells. Note swollen endothelial cells. B = fused medial smooth muscle cells; C = rounding and clumping of nuclei; D = myocardium.

FIG. 6. Myocardial artery in posterior papillary muscle showing intimal fibrosis. Age 15 years. Inactive case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = fibrotic intima; B = hypertrophied media; C = intimal elastification in another vessel; D = myocardium.




Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

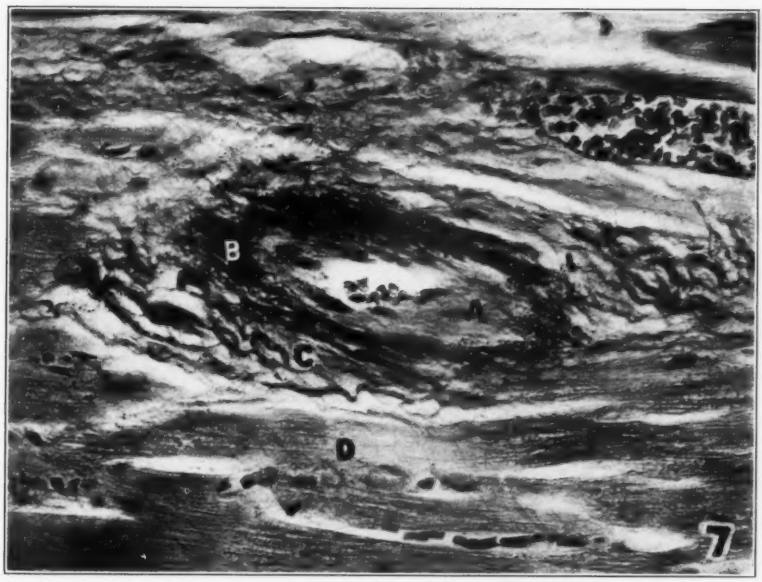
## PLATE 34

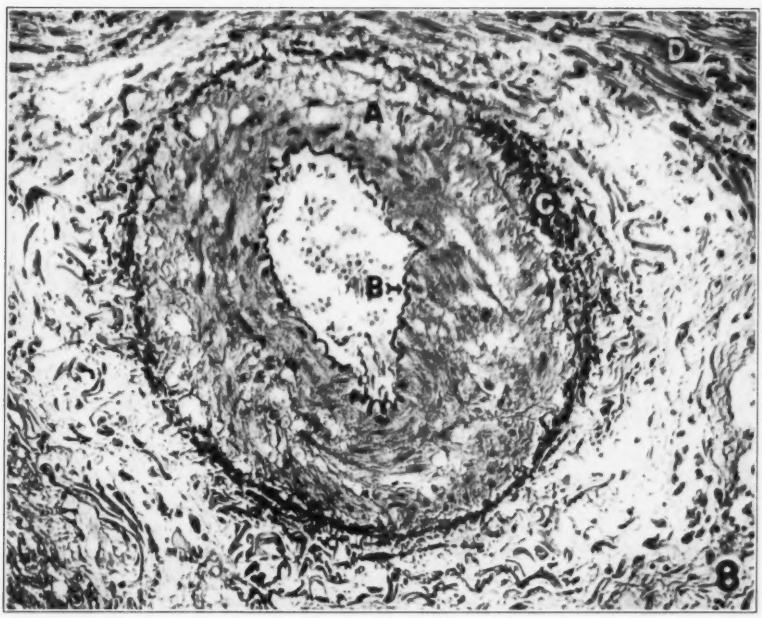
FIG. 7. Myocardial artery in posterior papillary muscle showing intimal fibrosis superimposed on intimal elastification. Age 36 years. Inactive case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = fibrotic zone situated internally to intimal elastified zone; B = intimal elastified zone; C = rather atrophic media; D = myocardium.

FIG. 8. Myocardial artery within the periaortic pericardial sheath showing giant medial hypertrophy with metallaxis. Age 15 years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = enormously hypertrophied and markedly edematous media with disorientation of smooth muscle fibers; B = lamella elastica interna; C = elastified adventitia; D = myocardium.




Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

## PLATE 35

FIG. 9. Myocardial artery in left ventricle showing exudative and necrotizing panarteritis. Age 25 years. Active case. High power. Hematoxylin and eosin stain.

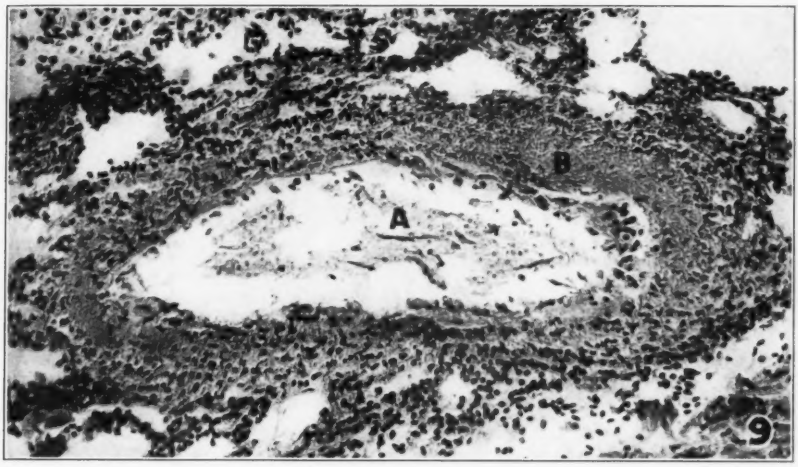
A = lumen of vessel containing red blood cells and desquamated endothelium; B = necrotic media. Note marked infiltration of adventitia and media with inflammatory cells.

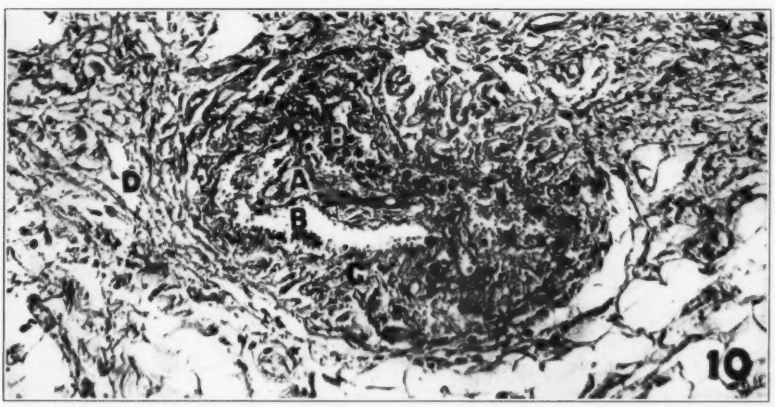
FIG. 10. Myocardial artery in myo-epicardial wedge of right auricle showing subendothelial hemorrhagic arteritis. Age $3\frac{1}{2}$ years. Active case. High power. Hematoxylin and eosin stain.

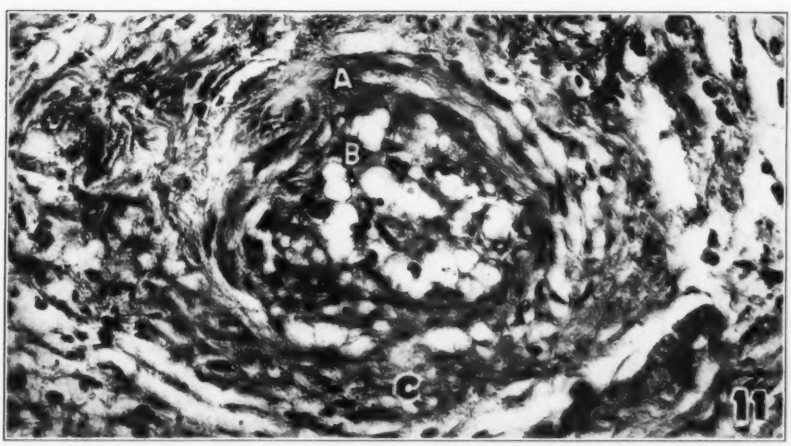
A = extremely narrowed lumen of vessel containing hyaline thrombus and lined with endothelial cells; B = subendothelial space containing red and white blood cells; C = disrupted media; D = adventitia.

FIG. 11. Myocardial artery in myo-epicardial wedge of right auricle showing net-like fibrinous thrombosis. Age $3\frac{1}{2}$ years. Active case. High power. Hematoxylin and eosin stain.

A = markedly edematous media; B = net-like strands of fibrin producing incomplete occlusion of the vessel; C = adventitia.


B
A
9


B
D
A
B
C
10


A
B
C
11

## PLATE 36

FIG. 12. Myocardial artery in left ventricle showing endarteritis verrucosa. Age $4\frac{1}{2}$ years. Active case. Medium power. Hematoxylin and eosin stain.

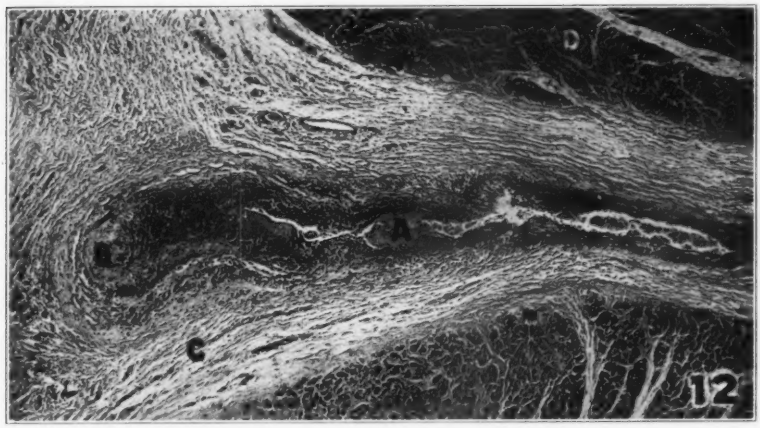
A = typical verrucous lesion; B = remains of media; C = adventitia; D = myocardium.

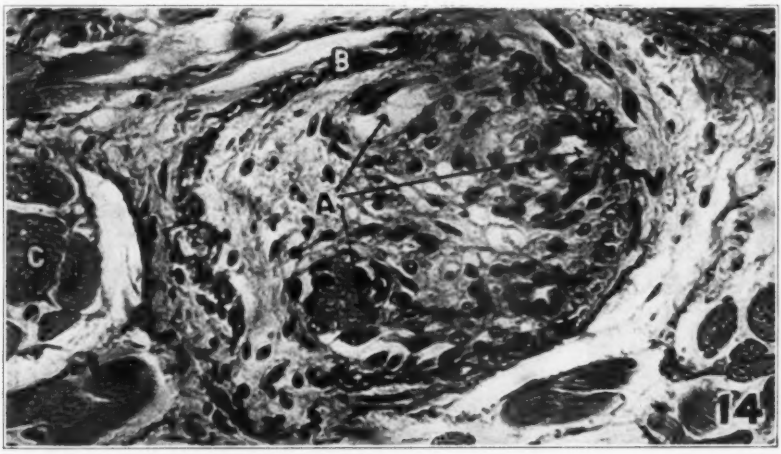
FIG. 13. Small myocardial arteries in posterior wall of left ventricle showing granular plugged vessels. Age 38 years. Active case. High power. Hematoxylin and eosin stain.

A = typical granular plugged vessel; B = small canalized vessel; C = myocardium.

FIG. 14. Myocardial artery in posterior wall of left ventricle showing canalization. Age 38 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = obliterated lumen containing three vascular canals; B = elastified adventitia; C = myocardium.






Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

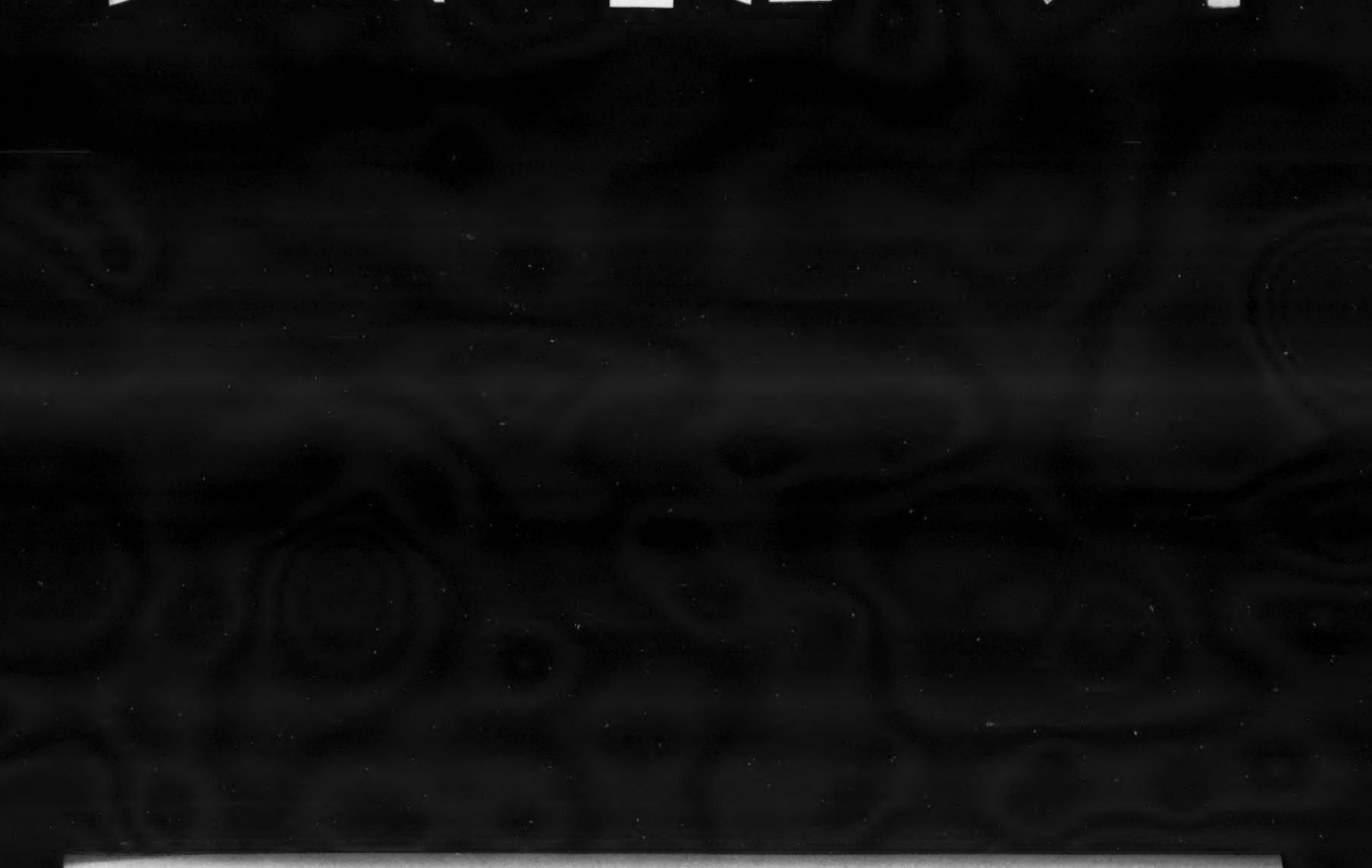
PLATE 37

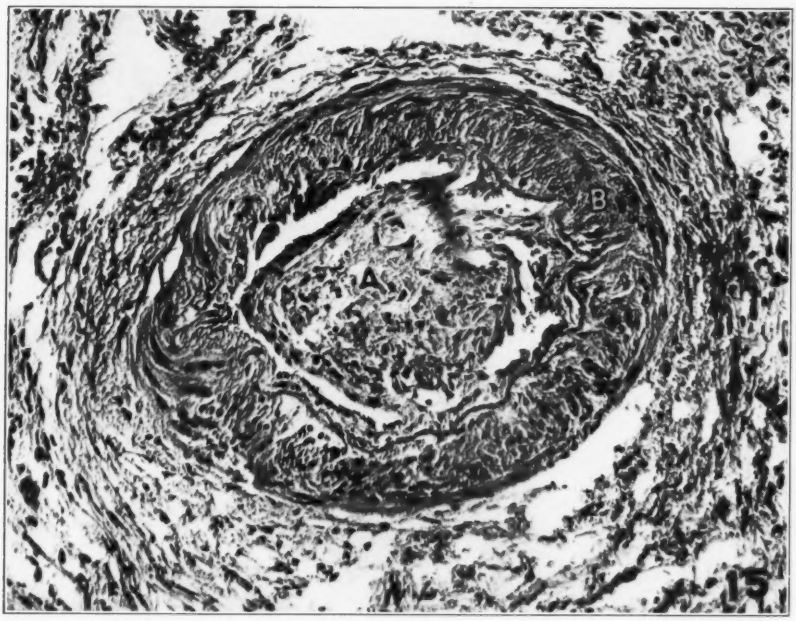
FIG. 15. Myocardial artery in posterior wall of left ventricle showing endarteritis polyposa. Age 17 months. Active case. High power. Hematoxylin and eosin stain.

A = centrally placed, organizing polypoid mass within the lumen of the vessel; B = media.

FIG. 16. Myocardial artery in the left auricular retro-aortic myo-epicardial wedge showing intimal musculo-elastic hyperplastic lesion (concentric type). Age 13 years. Active case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = raised endothelium; B = intimal musculo-elastic hyperplastic layer showing cross-section of longitudinal smooth muscle cells surrounded by mantles of elastic tissue; C = additional inner zone showing early musculo-elastic hyperplastic changes and possibly representing fresh attack; D = markedly edematous media; E = adventitia.




A
B
15

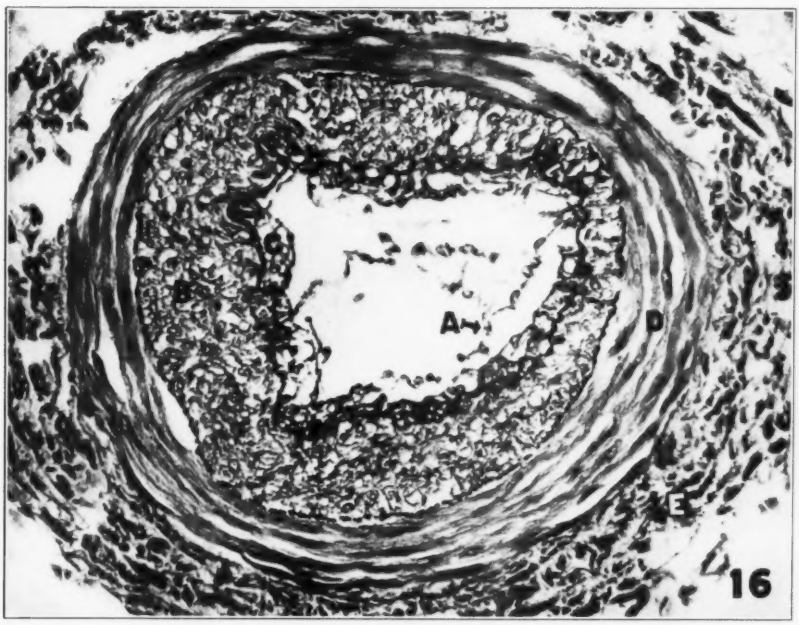

A
B
D
E
16

PLATE 38

FIG. 17. Myocardial artery in interventricular septum showing intimal musculo-elastic hyperplastic lesion (eccentric type). Age 11½ years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

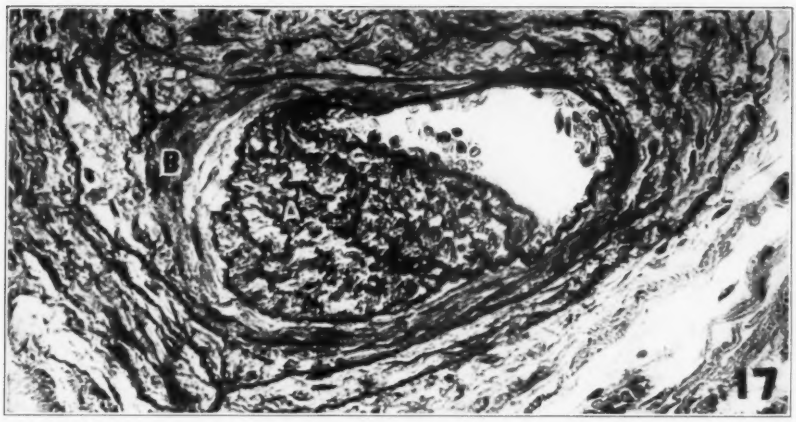
A = eccentrically placed, intimal musculo-elastic hyperplastic lesion consisting of longitudinal smooth muscle cells surrounded by elastic mantles. Note somewhat laminated appearance. B = media.

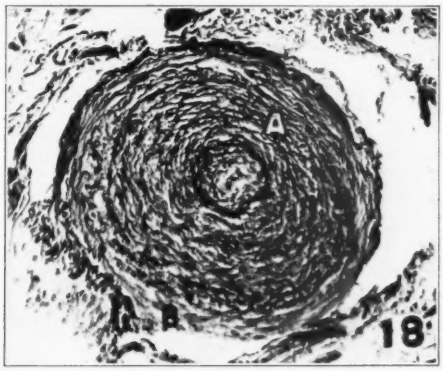
FIG. 18. Myocardial artery in the left auricular retro-aortic myo-epicardial wedge showing end result of intimal musculo-elastic hyperplastic lesion. Age 30 years. Inactive case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

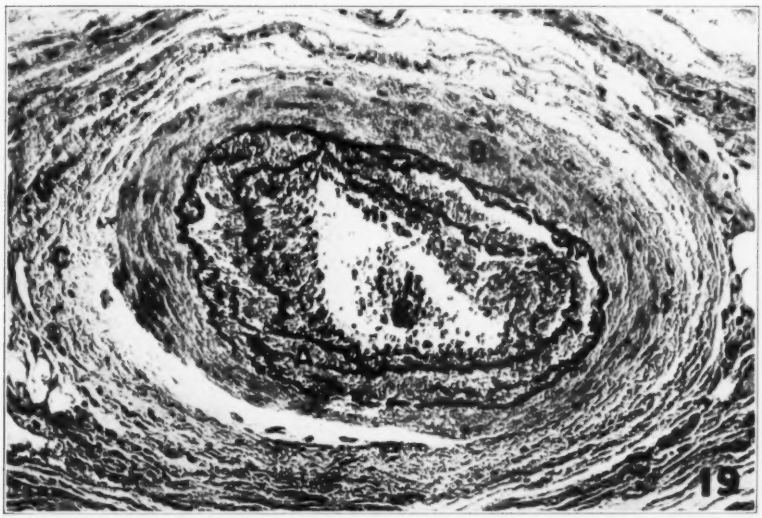
A = lumen almost completely obliterated by markedly elastified intima. These elastic fibers, together with collagenous material, have almost completely replaced the longitudinal smooth muscle cells of the intimal musculo-elastic hyperplastic lesion. B = media.

FIG. 19. Myocardial artery in interventricular septum showing intimal musculo-elastic hyperplastic lesion (laminated type). Age 30 years. Inactive case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = laminated musculo-elastic hyperplastic lesions, possibly representing different attacks; B = media; C = adventitia.


B
A
17


A
B
18


B
A
19

## PLATE 39

FIG. 20. A group of vessels situated in the left auricular retro-aortic myo-epicardial wedge showing various characteristic lesions. Age 18 years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

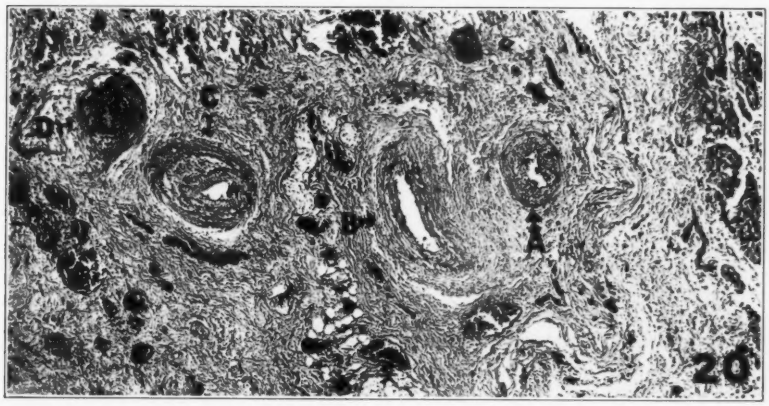
A = vessel showing intimal musculo-elastic hyperplastic lesion; B = vessel showing intimal fibrosis; C = vessel showing intimal fibrosis with some elastification; D = vessel showing giant medial hypertrophy with metallaxis.

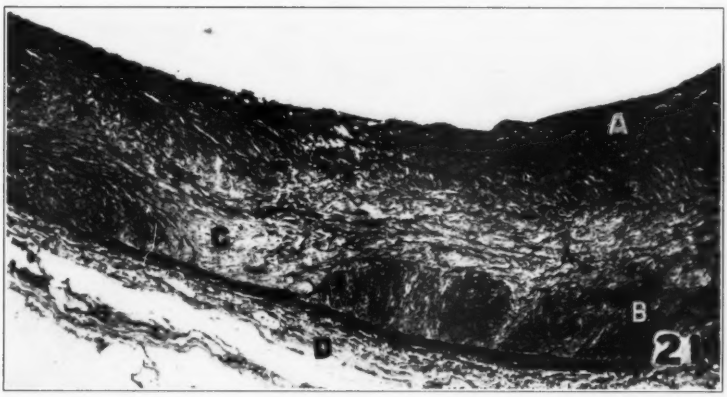
FIG. 21. Left anterior descending coronary branch showing scarring and elastification of media. Age 38 years. Inactive case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

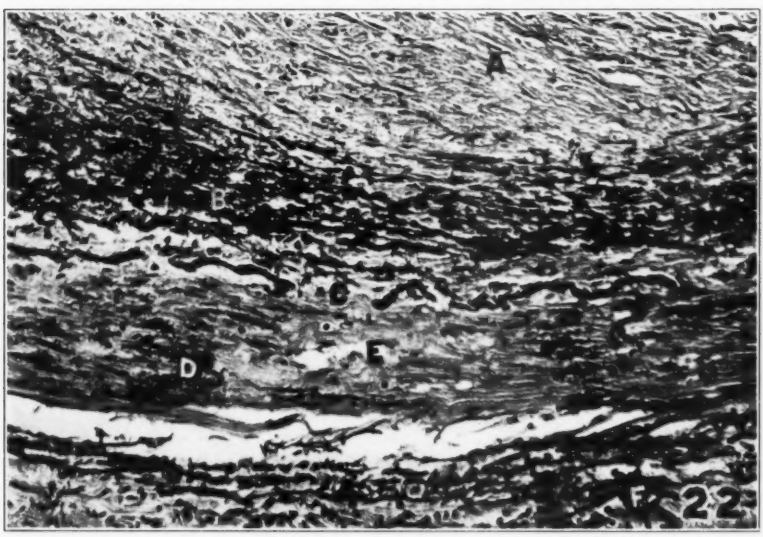
A = elastified intima; B = distorted, heavily elastified patches in markedly elastified media; C = scarred area in media; D = adventitia.

FIG. 22. Left anterior descending coronary branch showing scarring and elastification of media. Age 50 years. Inactive case. High power. Weigert's elastic and Van Gieson's connective tissue stain.

A = fibrotic layer of intima; B = elastic-hyperplastic layer of intima; C = discontinuities in lamella elastica interna; D = heavily elastified media with splitting and fraying of elastic membranes; E = conspicuous scar in media with replacement of smooth muscle by connective tissue; F = adventitia containing scattered lymphocytes.




Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

PLATE 40

FIG. 23. Right circumflex coronary artery showing fibrotic intima and edematous media. Age 14 years. Active case. Medium power. Hematoxylin and eosin stain.

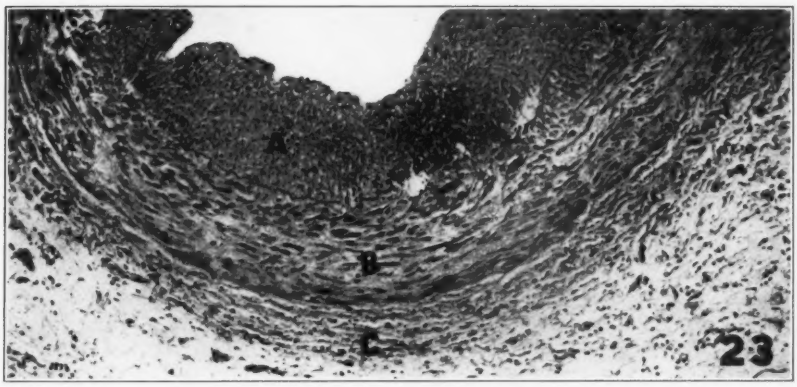
A = fibrotic thickened intima; B = marked edema of media; C = adventitia.

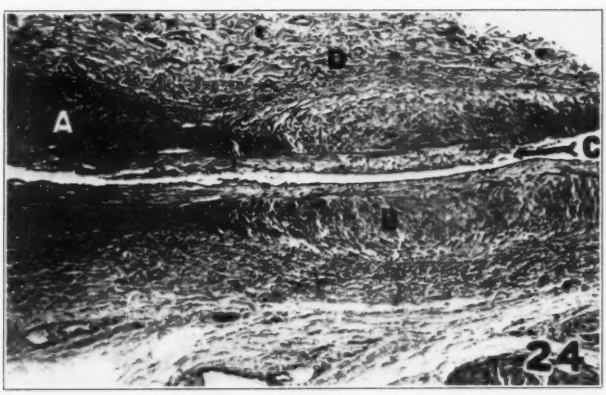
FIG. 24. Right circumflex coronary artery showing inflamed edematous media and intimal reduplication. Age $4\frac{1}{2}$ years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = normal portion of media showing compact smooth muscle; B = swollen and edematous portion of media with inflammatory cells; C = recently formed reduplicated layer; D = adventitia.

FIG. 25. Left anterior descending coronary branch showing edema of media and dissolution of lamella elastica interna. Age $3\frac{1}{2}$ years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = disappearance of lamella elastica interna; B = edematous media with swelling and prominence of medial cells; C = adventitia; D = myocardium.


A
B
C
23


D
A
C
B
24

D
C
B
A
25

## PLATE 41

FIG. 26. Left circumflex coronary artery showing necrotizing arteritis in case of periarteritis nodosa with rheumatic fever. Age 7½ years. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

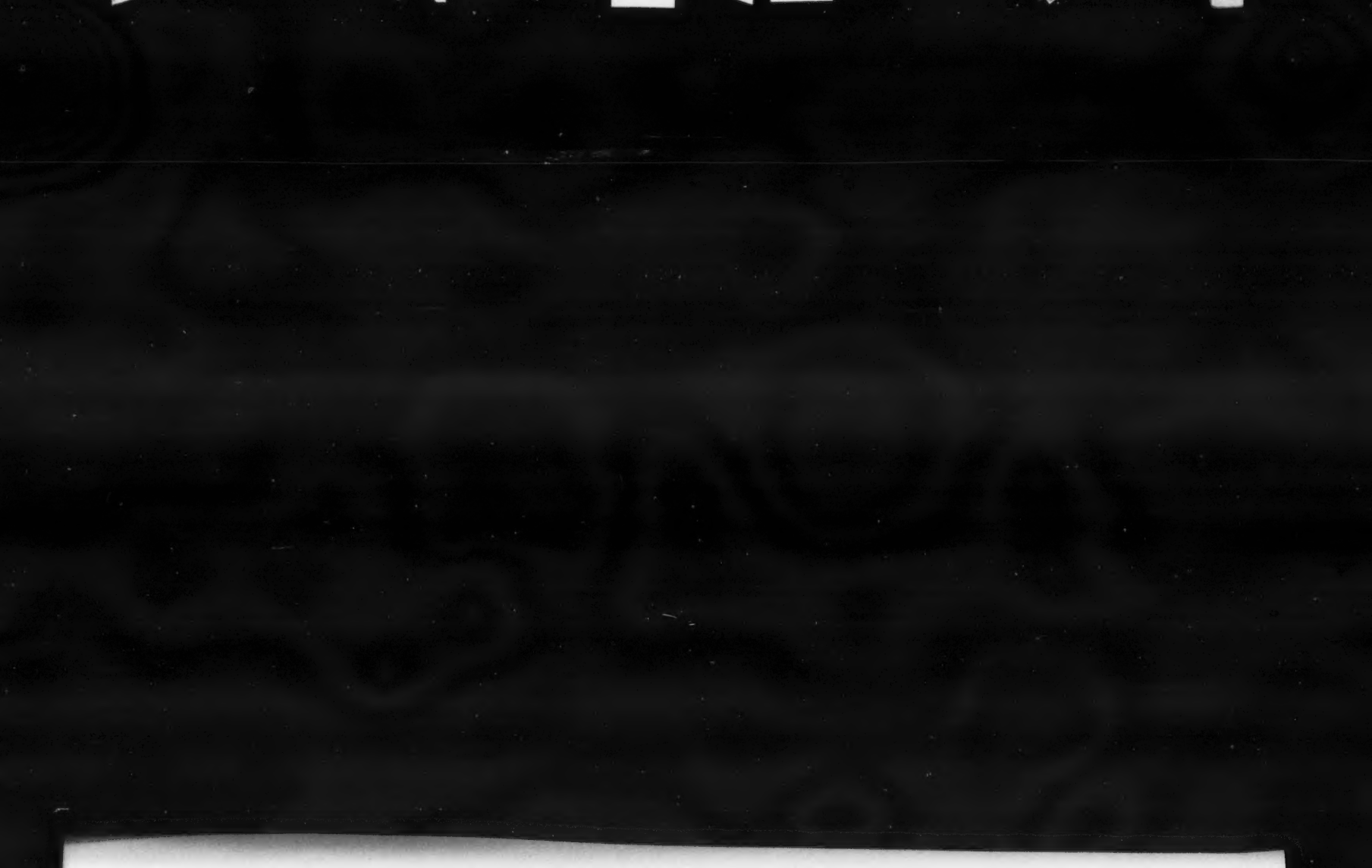
A = markedly edematous and inflamed media; B = rupture and dissolution of intimal elastic membranes; C = rupture, fraying and dissolution of adventitial elastic membranes; D = blood-platelet thrombus; E = elastic-hyperplastic intima; F = adventitia.

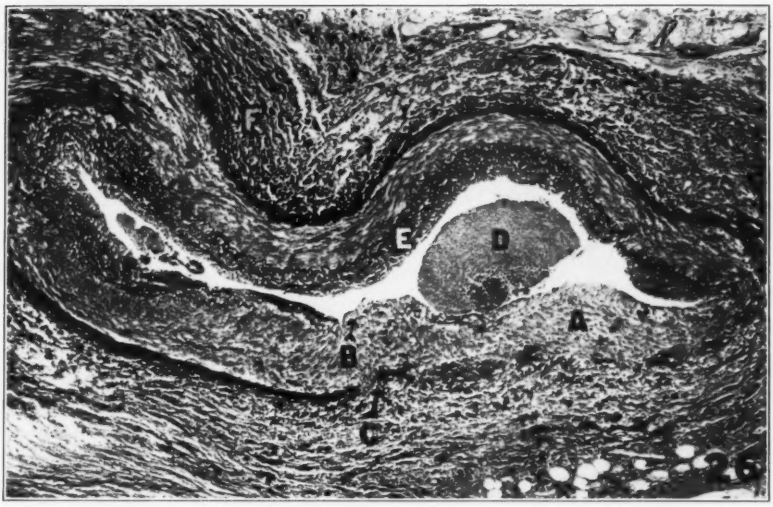
FIG. 27. Thrombosis of left circumflex coronary artery. Age 17 months. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

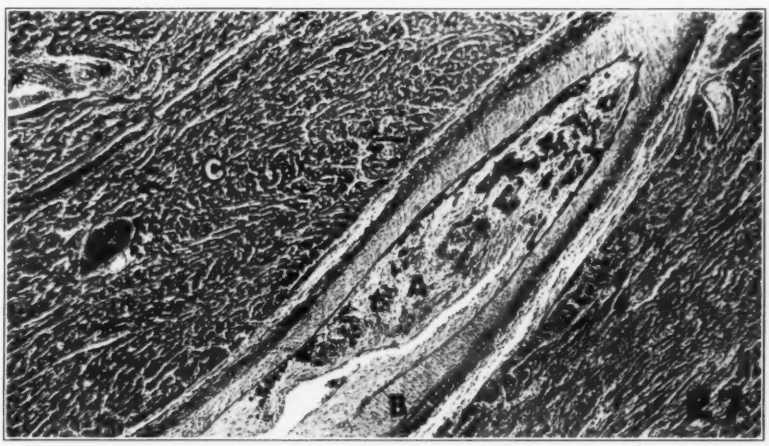
A = lumen of vessel almost completely occluded by blood-platelet thrombus; B = media; C = myocardium.

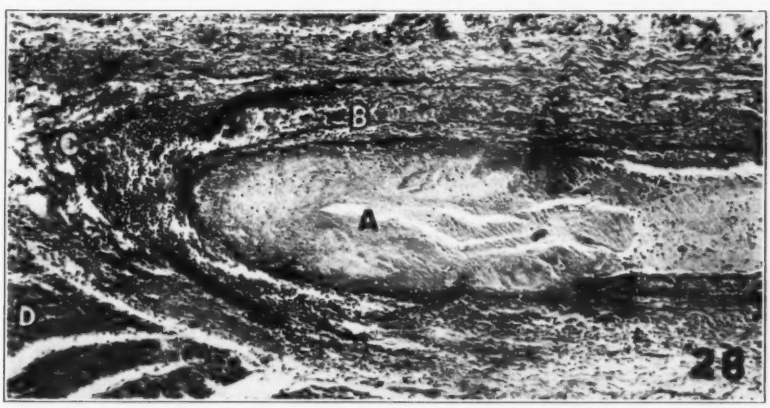
FIG. 28. Left circumflex coronary artery showing arteritis and occluding granular plugged lesion. Age 25 years. Active case. Medium power. Weigert's elastic and Van Gieson's connective tissue stain.

A = granular plugged lesion occluding lumen; B = edematous inflamed media; C = markedly inflamed adventitia; D = myocardium.






Gross, Kugel and Epstein Lesions of Coronary Arteries in Rheumatic Fever

# ENDOMETRIOSIS OF THE UMBILICUS *

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At the meeting of the American Association of Pathologists and Bacteriologists in Rochester, New York, in 1927, I described 2 cases of endometriosis of the umbilicus under the title of "Menstruating Umbilical Tumors." Several authors have since included these 2 cases in lists of the reported cases of this interesting condition, depending upon a brief abstract [1] for their information. In order to make more complete data available to others, these cases are now published in full for the first time.

In 1927, endometriosis of the umbilicus, or umbilical adenomyoma, as it was then more commonly called, was considered a very rare condition. About 35 cases had been described. In the next few years reports of this condition were numerous, so that by 1931 Spitz [2] designated his case as the 55th. There is no occasion to review the literature of these many cases at the present time. Spitz [2] has provided a comprehensive tabulation and Enzer,[3] in 1930, again brought the literature up to that date and discussed some of the more important questions that arise in connection with umbilical endometriosis.

Those who are interested in as complete a compilation as possible may add the following cases which are not referred to by either Spitz [2] or Enzer [3]: Terrier [4] (1887), Tourneux [5] (1889), Rohdenburg [6] (1919), Cullen [7] (1920) 2 cases, Walz[8] (1926), Butomo and Schereschewsky[9] (1930), Habbe [10] (1931), Thompson [11] (1931), Stetson and Moran [12] (1932), Siedentopf [13] (1932), Longwood [14] (1932), Herberz [15] (1933) 3 cases, and Lanos and Busser [16] (1933).

Our own cases, 2 in number, are as follows.

## CASE REPORTS

CASE 1 (2783–V). On May 18, 1918, there was delivered to the laboratory by an outside physician a mass which was said to be an

* Received for publication August 23, 1934.

umbilical tumor. It had been excised from a woman about 45 years of age. No history was obtainable other than that the patient had no children, although married for more than 15 years. A diagnosis of congenital umbilical cystadenoma was made and a brief description of the histological features was recorded.

After receiving the second case a number of years later the material from the first case was restudied. The gross material consisted of the umbilicus surrounded by an elliptical zone of skin. Centered beneath the umbilicus there was a firm nodular mass about 2 cm. in diameter. On section this was found to contain small spaces, the largest about 2 mm. in diameter. There was no evidence of hemorrhage in the interior of the mass.

Microscopic examination showed that the specimen was covered by skin on one side and by peritoneum on the other. The small cystic spaces, more than twenty of which appeared in a single section, occurred in a non-encapsulated mass which occupied almost the entire thickness of the wall. Over it, both corium and epidermis were intact. The cysts, of varying size and shape, were lined by a columnar epithelium which frequently showed cilia (Fig. 1). About this, in certain examples only, there was a richly nucleated and finely reticular stroma ("cytogenic stroma"), resembling the interglandular tissue of endometrium. In the largest cyst there were many phagocytes containing old blood pigment and a mass of well hemolyzed red blood cells. Outside of the cellular stroma, or immediately about those cysts around which such stroma was missing, there was fibrous connective tissue of varying density, some of which showed the usual appearance of the remains of the umbilical scar. There was no definite encapsulation of the mass but this somewhat atypical connective tissue passed rather abruptly into the normal stroma of the region. There was no involuntary muscle present other than that of the blood vessels. This opinion, based originally on routine hemalum and eosin stains, was confirmed by subsequent staining with Van Gieson's mixture. The large sweat glands of the region occurred near, but not within, the nodular mass.

The gross and microscopic features were thus characteristic in every respect of endometriosis of the umbilicus.

Case 2 (2788–AE). An American housewife, 49 years of age, was referred to the general surgical service from the out-patient department with a diagnosis of questionable melanoma of the um-

bilicus. The patient had been married twice. She had had six children by her first husband, none by the second. About 2½ years before coming to the hospital she had noticed a small painful swelling in the umbilicus. This was not preceded by trauma nor could she recall having had a mole at that site. The tumor had slowly increased in size and the patient stated that there had been some oozing of blood at the time of the menstrual periods only. Those who first examined her were inclined to discredit this assertion, but with the appearance of the menses while she was still in the hospital such oozing of blood did occur.

Examination of the patient showed at the umbilicus two protruding nodules, each about 3.5 cm. in diameter. These were separated by a vertical fissure in the midline. The mass to the left was hard and its lower part was bluish black in color. The right portion was softer and pigmented but slightly. The umbilicus, with these nodules and a zone of skin, was excised with the endotherm knife. The peritoneal cavity was opened and a small portion of the preperitoneal fat removed with the mass.

On microscopic examination the greater part of each nodular mass was found to be made up of cystic structures of varying size, with cubical to columnar epithelium, the latter often ciliated (Fig. 2). Practically every one of these spaces had about its epithelial lining an investment of a cellular reticulum, exactly like endometrial stroma in a highly cellular phase. In many of the spaces there was recent hemorrhage, showing but little hemolysis. In others there were phagocytes containing older blood pigment. Outside of the zones of "cytogenic stroma" there was an abundant dense connective tissue such as is normally found at the umbilicus. There was no demonstrable connection between the peritoneum and the structures described. The epidermis was lacking, however, over a portion of the surface and here there was shallow ulceration and a secondary inflammatory reaction. Sweat glands were abundant and were to some extent intermingled with the cystic structures, but there was no evidence of any connection between the two. Smooth muscle was entirely lacking.

## Discussion

In addition to placing these 2 cases of umbilical endometriosis on record, it is desired to call attention to the fact that the propo-

nents of those theories of the origin of endometriosis that require implantation or metastasis of fragments of endometrium are confronted with serious difficulties in explaining its occurrence in this situation. Jacobsen [17] has stated that he believes that there are present in these cases small umbilical hernial sacs into which endometrial tissue that has been set free in the peritoneal cavity has found its way. While endometriosis has been described in connection with umbilical hernia (Mintz [18]), in most of the reported cases, as in our own, no evidence of umbilical hernia has been found. Also, if this is the explanation, it is surprising that endometriosis has never been described for any other peritoneal recess of the upper half of the abdomen, including the lesser peritoneal sac. Since at the umbilicus there is opportunity for a physiological inclusion of peritoneal mesothelium and subserosa, the advocates of the serosal theory of endometriosis have no difficulty with this localization, and endometriosis should have a single explanation no matter where it occurs.

## Conclusions

In conclusion, attention is invited particularly to the following points.

1. With over 70 cases described in medical literature the umbilicus can no longer be considered a rare location for endometriosis.

2. Smooth muscle is commonly not present in endometriosis of the umbilicus and is not an essential element in these formations. The term "adenomyoma" is altogether inappropriate.

3. The sweat glands, which have been mentioned repeatedly in connection with umbilical endometriosis, have no part in the genesis of this condition.

4. The origin of umbilical endometriosis is explainable only with the greatest difficulty under the implantation and metastasis theories, but is readily understandable under the various modifications of the serosal theory.

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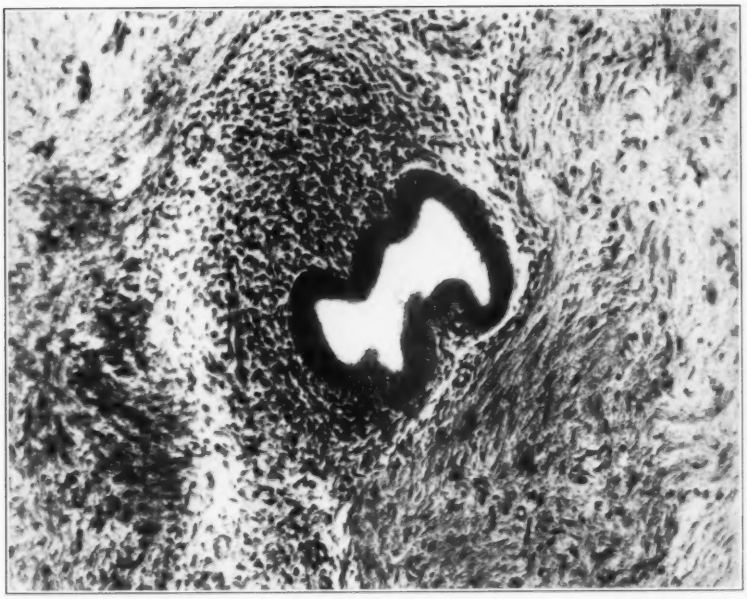
## DESCRIPTION OF PLATE

### PLATE 42

FIG. 1. Case 1. Umbilical endometriosis. Ciliated columnar epithelium surrounded by a richly nucleated spindle-celled stroma. This in turn is embedded in a dense connective tissue without smooth muscle. Hemalum and eosin stain. × 156.

FIG. 2. Case 2. Umbilical endometriosis. A menstruating umbilical tumor. Structure is the same as in Case 1. In addition some of the gland spaces show recent hemorrhage. × 156.



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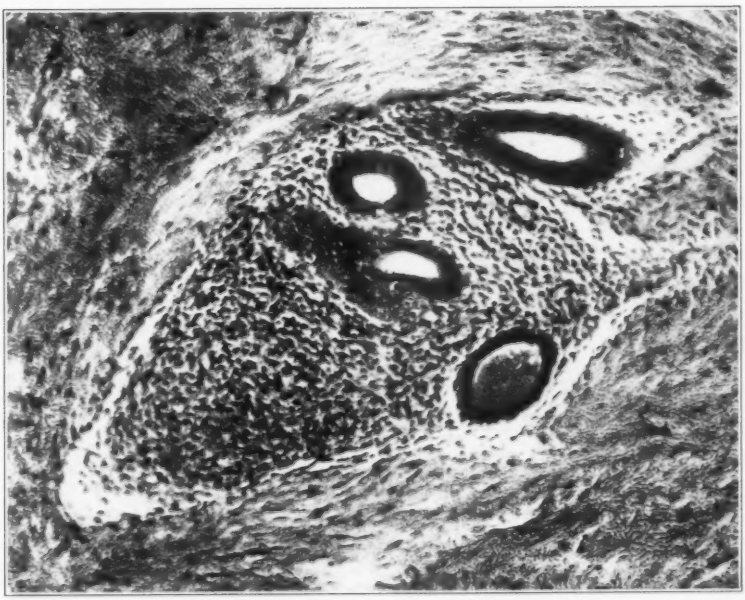

2

# THE ECTOPIC DECIDUAL REACTION AND ITS SIGNIFICANCE IN ENDOMETRIOSIS *

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Almost all pathologists whose duties include the routine examination of a large amount of surgical material are familiar with the nodular or plaque-like decidual reaction of the subserosa which not infrequently makes possible the diagnosis of pregnancy from an appendix. This condition was first described for the pelvic peritoneum in 1887 by Walker [1] in connection with extrauterine pregnancy. His findings were confirmed by numerous observers, some of whom found a serosal decidual reaction to be present in intrauterine pregnancy as well. The area in which this change was known to occur was enlarged during this period by finding it upon the ovary, oviduct, broad ligament, anterior rectal wall, small intestine where adherent in the pelvis, and the omentum where adherent to an oviduct in which there was an ectopic gestation. The literature of this phase was reviewed by Hirschberg [2] in 1905, who then described for the first time the decidual reaction upon the appendix. This observation has been confirmed repeatedly, until now knowledge of it has become a necessary part of the armamentarium of the pathologist. In an active diagnostic service several examples may be seen in a single year.

Upon the appendix the decidual reaction appears as small nodules, streaks and patches produced by a thickening of the serosa or, more properly, the subserosa. These nodules are frequently mistaken by the surgeon for tubercles, metastatic neoplasm or organizing exudate. The microscopic appearance is characteristic and may be taken as a type form for this reaction wherever found (Figs. 1 and 2). Beneath an intact mesothelium and apparently developing from the stroma cells of the subserosa, nests of large cells with slightly basophilic cytoplasm and spherical, usually eccentric, nuclei occur. These large cells, often 30 microns or more in diameter, resemble in

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every respect the decidual cells of endometrial origin. Geipel [3] has shown that, like intrauterine decidual cells, the peritoneal counterpart is often richly supplied with glycogen.

After Hirschberg, there were further significant extensions of the area in which the serosal decidual reaction was known to occur. The literature of the intervening period is reviewed by Rosenberger.[4] Attention is directed particularly to the demonstration of the ectopic decidual reaction in pelvic lymph nodes by Geipel.[5] In some of the same lymph nodes duct-like or gland-like spaces lined by cubical or low columnar epithelium were found. At the present time such areas would be interpreted, in all probability, as endometriosis with a secondary decidual reaction. In a later paper Geipel [3] reported the occurrence of the decidual reaction upon the diaphragm and the splenic capsule.

Decidual reaction in the cervical mucosa has been observed repeatedly. It is especially apt to occur with placenta previa. Róna [6] has described a decidual reaction at the external os; and the development of such an excessive decidual formation in the vaginal wall as to merit the name of *polyposis vaginae* has been reported by Zacherl.[7] While his excellent illustrations show glands of cervical type to be present, those glands about which the decidual reaction occurs are of a different type and the entire complex suggests a decidual reaction taking place in an area of endometriosis. Yet Zacherl believed that endometriosis could be excluded.

In an especially uncertain position is the question of a possible ectopic decidual reaction without either intra- or extrauterine pregnancy. In all the examples to which reference has been made above, pregnancy was present. But Schiller[8] and Schereschewsky[9] have shown the development of decidual formations in the apparent absence of pregnancy. Whether this is another manifestation of *decidua menstrualis* and is comparable to the premenstrual changes in the endometrium, or whether the fact of pregnancy escaped detection in the reported cases, cannot be determined positively at the present time.

Endometriosis has been described for the uterine wall, oviduct, ovary, mesovarium, broad ligament, round ligament, vagina, cervix, bladder wall, rectum, sigmoid colon, cecum, mesocolon, appendix, small intestine, retroperitoneal and inguinal lymph nodes, umbilicus and laparotomy scars (*Lit.* by Jacobsen,[10] Polster[11]). It will at once

be noted that, with few exceptions, the regional distribution of endometriosis coincides with that of the ectopic decidual reaction. The only significant difference is in the reported occurrence of a decidual reaction upon the diaphragm and the splenic capsule. Apparently, endometriosis has never been noted as occurring above the level of the umbilicus. It is possible to go even farther in the comparison, for there is a similarity in the relative frequency of occurrence of the two conditions in various regions. Polster found in a collection which included over 1000 cases of endometriosis of the ovaries, tubes and uterine ligaments, 90 in the rectovaginal septum, 80 in the intestinal tract, 56 in scars, 34 in the inguinal regions and 30 at the umbilicus. In a general way, the incidence decreases as the distance from the ovaries increases, as is true of the ectopic decidual reaction. If the analogy from distribution of the two conditions is as significant as it appears to be, the very rare occurrence of the, as yet, unknown endometriosis of the diaphragm may be predicted.

In addition to the similarity in regional distribution between endometriosis and ectopic decidual formation, which was noted as early as 1925 by Schiffman and Seyfert,[12] there are other significant features. Geipel [3, 5] found that glandular spaces were frequently present in the retroperitoneal nodes showing an ectopic decidual reaction. Conversely, a decidual reaction has been described for the "cytogenic" stroma of endometriosis in almost every location, including umbilicus, cervix and vagina. The "cytogenic" stroma of endometriosis is the interglandular stroma of the endometrium. They function alike in the development of decidua. But, under appropriate hormonal stimulation, exactly similar decidual cells may develop from the cellular elements (apparently of the connective tissue group) which lie immediately beneath the serosal cells proper over a wide area in the lower abdomen and pelvis.

Such similarities and identities of morphology and function support the serosal theory of origin of endometriosis. The subserous stromal cells must possess pluripotentiality in differentiation. Under the influence of suitable but dissimilar stimulation either the "cytogenic" stroma of endometriosis or the decidual reaction may result. If the former develops, it in turn may subsequently be induced to become decidual. In the decidual reaction the mesothelial cells do not appear to take any part. They lie apparently unchanged on the

masses of decidual cells. While not properly germane to the subject of this paper, it must be assumed that the surface mesothelial cells likewise possess latent potentiality in differentiation and that from them, particularly when entrapped in adhesions or in scar tissue, and again under stimulus of a hormone, the epithelial elements in endometriosis are derived.

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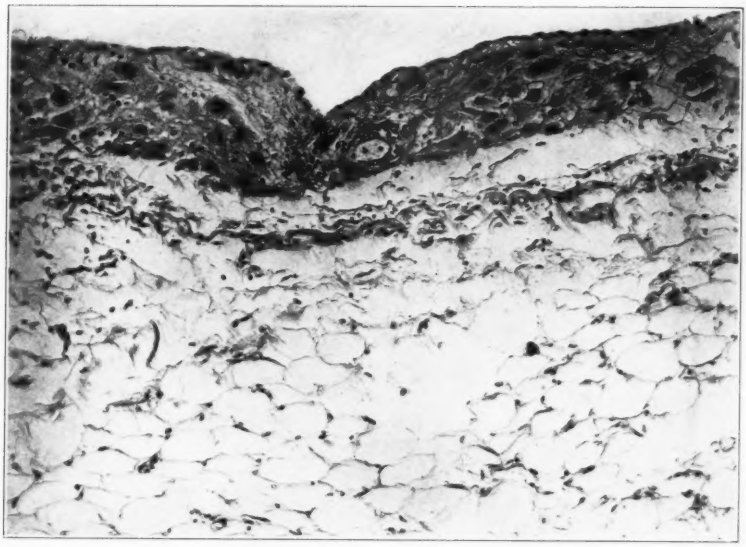
## DESCRIPTION OF PLATE

### PLATE 43

FIG. 1. Decidual reaction in the subserosa of the meso-appendix, in the fifth month of pregnancy. Hemalum and eosin stain. × 198.

FIG. 2. Decidual reaction in the subserosa of the appendix, from the same case as the preceding. × 310.



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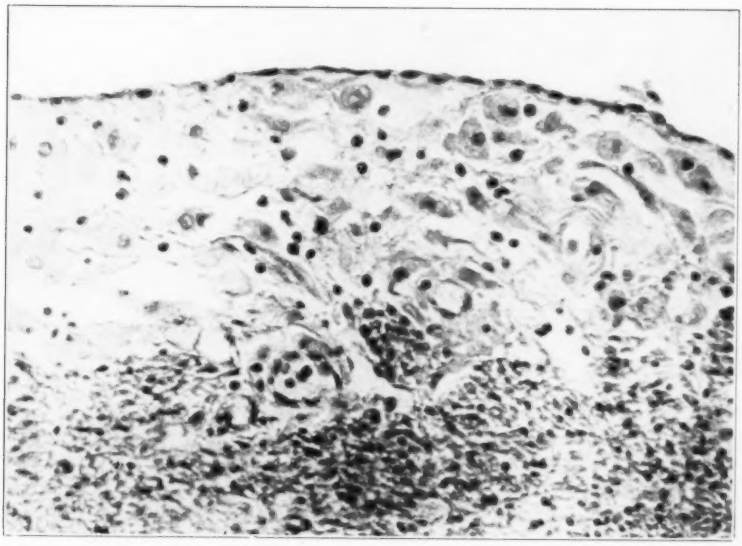

2

# DIFFUSE ARTERITIS OF SYPHILITIC ORIGIN *

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That the *Treponema pallidum* may cause arteritis has long been recognized. The aorta and cerebral vessels are involved most frequently, although lesions in small vessels elsewhere, such as those of the extremities, have been found occasionally. This subject was reviewed recently by Connor [1] in his Billing's lecture entitled "Development of Knowledge Concerning Role of Syphilis in Cardiovascular Disease." In this lecture Connor noted how infrequently organisms have been found in the lesion.

Since we have had an opportunity to study both clinically and at autopsy a case with widespread involvement of the smaller arteries, and since the *Treponema pallidum* has been identified in one of these vascular lesions, it seemed wise to report our findings in some detail.

## REPORT OF CASE

*Clinical History:* The patient, a 26 year old male, was admitted for the first time to the hospital in January, 1933. At that time he complained of a painful sore on the penis of 7 days duration and of a urethral discharge. His past history was irrelevant, except that he had had gonorrhoea 6 years previously. He stated that he usually went on an alcoholic debauch monthly for 24 hours, at which time he was exposed sexually. The last occasion was 6 weeks previously.

Examination revealed a normal male, except for a chancre 1.7 by 1 cm. on the penis just back of the corona, and the presence of a moderately profuse urethral discharge. The discharge contained numerous organisms typical of the gonococcus. Scrapings from the ulcer, when examined by the dark field method, contained numerous treponemata. The patient remained in the hospital for 14 days, during which time he received five intravenous injections of arsphenamine. The dosage ranged from 0.1 gm. to 0.4 gm.

Following the last injection the patient had an erythematous dermatitis, due presumably to the arsphenamine medication. From this time until Aug. 18, 1933, the patient received three series each of arsphenamine and mercury succinimide in our Out-Patient Department. Hinton and Wassermann tests were repeatedly negative after April 4, 1933. He was treated for urethritis in the Genito-Urinary Department. On August 21, 1933, he was found to have a bilateral epididymitis. The patient was not seen again until Oct. 30, 1933, when

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he returned complaining of pain in the left calf and foot. This pain was shooting in nature and aggravated by walking. Examination at this time revealed no objective evidence of disease, such as swelling, redness or tenderness.

He was seen again on Nov. 15, 1933, with the complaint that the pain in his foot had persisted. He stated also that he had lost weight, had a poor appetite and was constipated. In January the patient weighed 188 pounds; his weight now was 153 pounds. Examination again revealed nothing abnormal, except for evidence of loss of weight and a chronic urethritis. His blood pressure was not recorded at this time. A roentgenogram of the left foot revealed slight atrophy of bones but nothing otherwise abnormal.

He was readmitted to the hospital as an emergency case on Dec. 4, 1933. Because of his confused, irrational state the interval history had to be obtained from his sister. The latter stated that the patient had had severe headaches for 1 week for which he had taken numerous "anacin" tablets and that he had taken twenty-eight tablets the day previously. Each "anacin" tablet contained three grains of acetophenetidin. Headache had persisted in spite of medication, and he had become very irritable and nervous. The morning of admission his vision became involved so that he could distinguish light from dark only.

Physical examination was unsatisfactory on account of the irritability and uncoöperative attitude of the patient. His blood pressure was 230 mm. mercury systolic and 100 mm. diastolic, whereas in January, 1933, it was 110/75 mm. of mercury. The heart seemed normal in all respects, and the walls of the peripheral vessels were not thickened. He was able to count fingers correctly at four feet. Although ophthalmoscopic examination was not satisfactory, no abnormality could be found other than a questionable blurring of the disc margins. All neurological reflexes were normal. The temperature was 100° F. and white blood cell count 12,000 per cmm.

Lumbar puncture at this time revealed a clear, colorless fluid under increased pressure. The fluid contained thirty lymphocytes and nine polymorphonuclear leukocytes per cmm. and an increased amount of globulin. Wassermann reactions on both blood and spinal fluid were negative.

Forty-eight hours after admission the patient seemed normal except for a slight persistent headache. Another lumbar puncture revealed only slight increase of pressure. The fluid at this time contained four lymphocytes per cmm. and a normal amount of globulin. The blood pressure had fallen gradually to 145 mm. mercury systolic and 98 mm. diastolic.

The patient's condition seemed to improve until Dec. 11, 1933, when he complained of cramp-like pain across the upper abdomen. This was accompanied by hiccough and periodic vomiting. Although tender to pressure there was no rigidity of the abdominal wall. At this time the white blood count showed 39,500 leukocytes per cmm. He was seen by Dr. Cutler, who could find no indication for surgical intervention. A stool, which had been free of blood previously, now contained blood in visible amount. The explanation for this was uncertain as the patient had internal hemorrhoids as a possible source. The red blood cell count and hemoglobin were normal and blood urea nitrogen was 21 mg. per cent. Another lumbar puncture was performed, which showed a considerable increase in pressure but nothing otherwise abnormal. With the persistence of nausea, vomiting and hiccough his condition grew worse gradually so that by Dec. 18, 1933, he was in a semicomatose state. At this time there was definite edema of the optic nerve heads, numerous areas of

hemorrhage in the right fundus oculi and incontinence of urine and feces. In view of the possibility of an intracranial tumor he was transferred to the surgical service where ventriculography and encephalography were performed with inconclusive results. His condition failed to improve and he died on Dec. 21, 1933. During the final 10 days of his illness seven white blood cell counts were done. The values of these ranged from 20,000 to 39,500 cells per cmm. His temperature at no time was above 100° F.

In view of the protean manifestations, a hypertension of rapid onset, hemorrhages into the retina, a probable mesenteric thrombosis, pains of unexplained etiology in an extremity, and a marked leukocytosis with little or no febrile response, the clinical diagnosis of vascular disease with multiple thromboses was made.

## Autopsy Report

Autopsy was performed 2 hours after death with the following findings.

*Body:* The body was that of a moderately well developed and well nourished white male, 172 cm. in length. Pitting edema of the lower extremities was present. There was a bilateral external strabismus. A small atrophic scar of the penis was found at the site where the primary chancre had been.

*Peritoneal Cavity:* The important findings will be considered in a discussion of the alimentary tract.

*Pleural Cavities and Mediastinum:* These regions were normal except for fibrous adhesions between the apex of the right lung and the parietal pleura.

*Heart:* The pericardial cavity was normal. The heart weighed 300 gm. There was a patent foramen ovale, which was 5 mm. in diameter. The four valves, myocardium and arteries were normal.

*Lungs:* The right lung weighed 700 gm. and the left 630 gm. In the lower lobe of each lung there were scattered and confluent, gray, nodular areas of pneumonic consolidation. Sanguinopurulent exudate could be expressed from these regions. The mucosa of the primary and secondary bronchi showed irregular areas of superficial necrosis covered by a grayish yellow fibrinopurulent exudate. There were no infarcts. The arteries and veins were normal.

*Celiac Axis and Branches:* The splenic, hepatic and left gastric arteries and their major branches appeared to have normal walls and lumens. The small branches of these major trunks will be described in connection with the organs which they supplied.

*Spleen:* The spleen weighed 300 gm. A few fibrous adhesions

were attached to the capsule. The pulp, trabecular structure and vessels were normal.

*Pancreas:* The pancreas weighed 110 gm. There were small indistinct areas of lobular fibrosis. Small arteries were prominent because of their thick, firm walls and very narrow lumens, several of which appeared to be occluded.

*Liver and Gall-Bladder:* The liver weighed 1800 gm. In the left lobe along the anterior border a subcapsular, well demarcated, yellowish white, friable area was found. This was roughly pyramidal in shape and 25 mm. in diameter. In this area the liver markings were not distinct but there was no evidence of liquefaction or caseation necrosis. Further incisions disclosed two small similar areas in the substance of the liver. The small intrahepatic arteries often had narrow lumens and thick walls. The veins were normal. No thrombi were found in the branches or tributaries of the portal vein.

The gall-bladder and extrahepatic biliary ducts were normal.

*Alimentary Tract:* The esophagus was normal. Along the lesser curvature of the stomach, midway between the cardiac and pyloric orifices, there was a punched-out, sharply circumscribed, circular ulcer measuring 8 mm. in diameter. The flat firm base and indurated margins of the ulcer were covered by dark red, necrotic material. In the first portion of the duodenum, just distal to the pyloric sphincter and on the posterior wall, a large irregular ulcer which measured 20 by 10 mm. was found. This appeared to be of more recent formation than the gastric ulcer. The remainder of the duodenum and the proximal 10 cm. of the jejunum were normal. The distal portion of the jejunum had numerous, punctate, subserosal and submucosal hemorrhages. There was slight mucosal edema but no ulceration.

In the ileum three principal areas of hemorrhagic infarction with mucosal ulceration were disclosed. Other similar though less severe lesions were present. The first large infarct was in the first portion of the ileum. The second lesion was 25 cm. distal to the first (Fig. 2). The third major lesion was 35 cm. proximal to the ileocecal valve. They were from 2 to 5 cm. in length and involved the entire circumference of the ileum as well as the adjacent 5 to 10 mm. of the mesentery. Although the degree of hemorrhagic gangrenous necrosis was different in each instance, the lesions were of similar character. The wall of the intestine varied in thickness in propor-

tion to the extent of edema, hemorrhage and necrosis, but in several areas of each infarct it was thin, friable, and greenish black in color. The second lesion was the most severe. A hemorrhagic, fibrinopurulent exudate had accumulated on the peritoneum and the loop of intestine was bound to the diseased sigmoid colon by fibrous and fibrinous adhesions. The mucosa in each area of infarction was hemorrhagic, edematous, soft and ulcerous. The ulcerations for the most part were adjacent to the attachment of the mesentery. They were shallow, poorly demarcated and often confluent. Their bases were flat and were covered with necrotic, gray, hemorrhagic material. The regional mesentery was slightly edematous and congested but had been spared the extensive necrosis that characterized the ileum.

The colon, except for that portion between the middle of the descending colon and the rectosigmoid junction, was normal. The involved part of the colon was contracted. Its wall and mesentery were thick and indurated. The mucosa was hyperemic and extensively ulcerated. The ulcers varied from 8 to 15 mm. in diameter. They were disposed circumferentially and tended to lie between the edematous rugae. They had irregular, well defined margins and gray, firm bases. The thick, edematous and often densely fibrous submucosa formed their bases. The cicatrization of the edematous, pericolonic fat, and the firm, fibrous adhesions which bound the small bowel to the colon indicated that the process was of subacute or chronic character.

The rectum was normal.

The direct cause of the lesions of the ileum and colon was disclosed by a dissection of the superior and inferior mesenteric arteries. The main channels and all branches of greater than 2 mm. in thickness were normal. The arcuate arteries of about 1 to 1.5 mm. in thickness often showed definite thickening of their walls, moderate narrowing of lumens and an unusual degree of adherence of the adventitia to the regional fat of the mesentery. These vessels, however, were much less seriously involved than were their terminal branches which passed directly to the ileum. The degree of involvement was not uniform but varied from place to place along the intestine and from place to place in the same artery. The arteries which supplied the jejunum were relatively free from changes. Those of the upper ileum that were abnormal were few in number. Along the remainder

of the ileum the vascular lesions were rather uniformly distributed, although there was a tendency for groups of arcuate branches to be more seriously diseased than their neighbors. This was especially prominent in the vascular tree which supplied the areas of infarction (Figs. 3 and 4). The branches supplying the colon were only rarely affected. These small arteries, which were usually 1 mm. or less in diameter, were often pale gray and firm, resembling fibrous cords. In other instances this resemblance was restricted to local areas, while a more normal vascular tunic persisted between the lesions. Often the only portion of the vessel that showed prominent thickening was at the point where the artery entered the wall of the ileum. There were no definite aneurysms, although isolated, small, nodular thickenings and spherical, purplish intravascular masses occasionally were found. Cross-sections showed that the appearance of the vessels was due to an increase in the thickness of the adventitia which was often abnormally adherent to the adjacent fat tissue, to a fibrous thickening of the media and intima and to partial or complete closure of the lumens by dense white tissue or firm red thrombi.

The inferior mesenteric, left gastric and pancreaticoduodenal arteries were inspected. The smallest vessels presented lesions that were identical with those of the small arcuate branches of the superior mesenteric artery. These were prominent among the branches that supplied the sigmoid colon and the first part of the duodenum but were rarely found elsewhere.

*Kidneys:* The right kidney weighed 180 gm., and the left 160 gm. They were of similar appearance. The capsules, which were of uniform normal texture, were adherent to the cortex in a few, small, depressed areas. The external surface of each kidney cortex was irregular in contour. There were numerous broad, slightly concave depressions which surrounded and merged imperceptibly with slightly convex, plateau-like elevations. The elevations varied from 1 to 15 mm. in diameter. They were irregular in outline and were usually firm and purplish red in color. Rarely, they were soft and grayish yellow. The intervening areas of cortical substance were firm and grayish pink. Coronal sections of each kidney showed a continuation of these variations in color and texture deeply into the cortex with a gradual diminution in diameter as the medullary regions were approached. The kidney markings were well preserved in the pale gray areas, indistinct in the purplish red zones and ab-

sent in the homogeneous, friable, grayish yellow parts of the cortex. The pyramids, pelves and calices were normal (Fig. 1).

The main renal arteries and their primary branches were normal. The interlobular arteries showed a variable degree of mural thickening with concentric narrowing of their lumens. These changes became greater in the distal parts of these arteries and in the arcuate arteries. Here, the lumens of the vessels occasionally were reduced to minute channels or were replaced by dense fibrous tissue, so that the arteries resembled solid fibrous cords. Thus it seemed that the alterations in the renal cortex represented the effects of partial or complete deprivation of arterial blood.

*Adrenals:* The right adrenal weighed 15 gm., and the left 10 gm. The small extracapsular arteries had thick walls and narrow lumens.

*Pelvic Organs:* Normal in appearance.

*Testes:* Except for a firm indurated hemorrhagic area (3 to 4 mm.) beneath the tunica of one testis, the testes were normal.

*Thyroid and Parathyroids:* The thyroid and parathyroids were normal.

*Bone Marrow:* The marrow of the ribs was dark red in color and slightly diminished in amount.

*Aorta:* Rare atheromatous patches in the intima of the abdominal portion of the aorta were seen.

*Eye:* The vessels were engorged. Moderate edema of the retina was present. Pin-point hemorrhages were few in number.

*Brain:* The brain weighed 1340 gm. There was slight flattening of convolutions and narrowing of the sulci of the cerebral cortex. An indistinct pressure cone was present at the base of the cerebellum. The meningeal and cortical hemorrhages were restricted to the sites of operative trauma. Coronal sections disclosed numerous small, grayish brown areas (1 mm.) in the cerebral cortex and subjacent white matter. The arteries and their branches showed no lesions.

## Microscopic Study

The sections were stained with eosin-methylene blue. The stains of Giemsa, Gram-Weigert and Levaditi were used in an attempt to demonstrate microörganisms.

*Heart:* The coronary arteries are normal. In the dense connective tissue adjacent to the adventitia of a small artery there is a

small area of infiltration with polymorphonuclear leukocytes and monocytes.

*Lungs:* All arteries are normal. An acute bronchitis and a confluent bronchopneumonia are present. Gram-positive diplococci are found in phagocytic cells. A few polymorphonuclear leukocytes are scattered throughout the walls of several veins.

*Spleen:* Except for a mild thickening and hyalinization of walls of arterioles, the arteries are normal. The sinusoids contain an increased number of polymorphonuclear leukocytes. A large amount of hemosiderin is found in mononuclear phagocytes. A hyaline, eosinophilic deposit is present in many follicles.

*Stomach:* There are lesions of the walls of submucosal arteries and ulcerations of the regional mucosa and submucosa. The lumens of the arteries are reduced to very narrow channels by proliferation of intimal cells and fibril formation. The newly formed intimal tissue is loose-textured and often infiltrated with polymorphonuclear leukocytes, plasma cells and lymphocytes. Occasionally, the intima is partially destroyed and thrombi fill the vascular lumens. In other arteries the process is less acute. In these instances cicatrization of the adventitia and media with lymphocytes scattered about in the dense connective tissue is found. The ulceration of the mucosa is acute. Edema, cellular infiltration and degeneration of tissues of the submucosa are noted in the base of the ulcer.

*Duodenum:* The ulcer is acute. There is extensive necrosis of the mucosa and submucosa. Thrombi of recent formation occlude many veins and arteries in the base and at the margins of the ulcer. The arteries of the submucosa, muscularis and serosa show pathological changes similar to those in the gastric arteries. The small arteries chiefly are affected by the disease. In the larger arteries intimal proliferation is predominant, and the vessel walls usually are free from inflammatory cell infiltration and fibrosis. The smaller arteries show less prominent intimal proliferation, old and recent thrombi, infiltration with lymphocytes and plasma cells and a variable degree of fibrosis of the media and adventitia.

*Small Intestine and Mesentery:* Numerous sections through the small intestine and its mesentery, both in the regions of the infarcts and of the grossly normal bowel, were studied. The significant findings are those in the walls of arteries and those of infarction of the ileum. The arterial lesions, which are common in the mesentery

and rare in the wall of the ileum, are inflammatory and chronic in character. The small arteries of less than 1 mm. in diameter principally are diseased. The smallest arteries, arterioles, and veins are normal or only secondarily affected. The greatest number of arterial lesions are healed. Several apparently are of chronic progressive character. None is acute. So far as could be determined, the earliest lesion seems to be characterized by an infiltration of polymorphonuclear leukocytes, plasma cells, lymphocytes and eosinophiles in the adventitia and outer portions of the media. Subsequent to, or coincident with, this reaction there is a proliferation of cells of the intima with deposition of delicate collagenous fibrils between the newly formed cells. This concentric proliferation is often so great that the narrowing of lumens is carried almost to the point of obliteration. In other instances degeneration of the inner layers of the intima and thrombosis has occurred. The various stages from acute thrombi to those which are dense, fibrous and canalized can be traced (Fig. 5). As the organization of thrombi progresses, there seems to be in the media a coincident atrophy and fibrosis accompanied by the appearance of small vascular channels. Cicatrization of the adventitia gradually becomes prominent. Numerous, small, endothelial-lined spaces are formed in the thick adventitia. These communicate through the newly formed capillaries in the media with the canaliculi in the thrombi. In several older lesions the cellular infiltration has disappeared, leaving the cicatrized remnants of the original arterial wall. There are several variations from this reconstructed sequence of pathological changes. The commonest variation is intimal proliferation which seems to be unassociated with inflammatory cell infiltration. The veins and large lymphatics show no primary lesions and only rarely are they seriously affected by the inflammation in the adventitia of the arteries which they accompany.

The wall of the ileum shows not only slight variations from normal histology but also extensive necrosis. In sections of normal ileum there is an occasional, small, submucosal artery which has a thickened intima and infiltrating lymphocytes and plasma cells in the adventitia. In the areas of necrosis, which may be considered as infarcts, arteritis is more widespread and severe. Not infrequently, acute and organized thrombi are found. In these regions there is an acute or subacute necrosis and a diffuse inflammation throughout the

entire wall. Usually the mucosa is destroyed. Beneath the ulcerations are many dilated vascular channels, several of which contain fibrinous thrombi. These thin-walled vessels extend through the acutely inflamed, edematous wall, ramify throughout the muscularis and serosa and anastomose with serosal vessels.

*Colon and Mesentery:* Numerous sections depict a process which is similar to that in the mesentery and wall of the ileum. The arteritis is of the same nature. The only appreciable difference between the infarcts is that in the colon there are several chronic, cicatrizing ulcers of the mucosa. In general, the lesions of the ileum are more acute.

*Liver:* In small arteries there are numerous inflammatory and proliferative lesions similar to those in the mesenteries, kidneys and elsewhere. The parenchyma is normal, except in the sections through the large pale area which is found along the anterior border of the liver. At the periphery of this well demarcated lesion small acute necroses are found in the midzonal regions. In the center of the area there is acute necrosis of the inner two-thirds of each lobule. The process is characterized by degeneration of liver cells, diminution in the number of red blood cells in the sinusoids, rare fibrinous thrombi in vascular channels and a large number of polymorphonuclear leukocytes, not only in sinusoidal spaces but also invading the columns of liver cells. This lesion is presumably an acute infarct which is the direct result of the arterial disease. In the periportal connective tissue and in Kupffer cells a moderate amount of hemosiderin is found.

*Pancreas:* There are numerous arterial lesions and old and recent infarcts. The type of arteritis is similar to that which has been described in the other organs (Figs. 6 and 7). Thrombi in all stages of organization are found. Several areas of acute or subacute necrosis and small intralobular cicatrices are present. These are probably secondary to partial or complete occlusion of the trophic arteries.

*Kidneys:* Arterial lesions and cortical infarcts are numerous. The inflammation of the arteries is either healed or of chronic progressive nature. The arteries which chiefly are affected measure less than 2 mm. in diameter. The interlobular and arcuate arteries show the most prominent changes. The smallest arteries, arterioles and glomeruli exhibit no primary lesions, although they are affected secondarily by closure of the vessels from which they arise.

The arterial disease is similar to that which is found especially in the mesenteries of the ileum and colon and in the pancreas. The largest arteries (2 mm.) show great thickening of the intima and a corresponding degree of reduction in the size of their lumens. This loose-textured, intimal hyperplasia is not associated with an inflammatory cell infiltration of the intima, except in those instances in which acute thrombi have formed. In the smaller arteries the fibrils and cells of the hyperplastic intima are in a more compact arrangement. The lumens are very narrow and often are occluded by old or recent thrombi. Recent thrombi are more common in the vessels of the kidney than elsewhere. However, the presence of organized and canalized thrombi, as well as the dense fibrosis of the media and adventitia, indicate that the disease is of long duration. In fact, there are only rare arteries which are infiltrated or surrounded by any significant number of lymphocytes and plasma cells.

The infarcts in the renal cortex are undoubtedly secondary to the arterial disease. As a rule, they are of acute nature and correspond to the elevated areas beneath the capsule of each kidney. Here, the glomeruli and tubules show a homogeneous necrosis without any appreciable disturbance of structural relations. The interstitial tissues are edematous and infiltrated with a few polymorphonuclear leukocytes. Infarcts of less recent date are represented by small radial cicatrices.

*Adrenals:* There are prominent pathological changes which involve the periadrenal tissues, the small arteries, the capsule, the sympathetic nerves and the cortex of each gland. The most significant lesions are those of the small arteries. These lesions consist of a proliferation of intimal cells in concentric fashion, an increase in the amount of collagen between the cells, marked narrowing of the lumens, organized and canalized thrombi, fibrosis of the adventitia and media and newly formed capillaries in the adventitia adjacent to the media. This process is accompanied by very little evidence of active inflammation. Occasional clusters of lymphocytes and plasma cells are found in the perivascular tissues and adventitia. The perivascular cicatrices which radiate from the adventitia involve the sheaths of several, unusually large, sympathetic nerve trunks. The fibrous capsule of each gland in many areas is dense and thick and portions of the glomerular zone are replaced by

cicatricial tissue. In the zona fasciculata there are acute and healed foci of degeneration. The acute lesions resemble the necroses in the liver. They show acidophilic, shrunken, cortical cells flanked by large numbers of polymorphonuclear leukocytes in the sinusoids. In the healed lesions most of the cortical cells have disappeared. Between the columns of residual atrophic cells there is an increased amount of connective tissue. In the medullary regions there are aggregates of sympathetic ganglion cells and large sympathetic nerve trunks.

*Testis:* Beneath the tunica albuginea there are several small arteries with lesions which do not differ from those in several other organs. These arteries contain several recent and a few organized thrombi. Focal areas of cicatrization and acute necrosis involve groups of seminiferous tubules. No significant changes are found in the arteries between the tubules.

*Thyroid:* The arteries and parenchyma are normal.

*Pituitary:* In the capsule of the anterior lobe there is an area of recent hemorrhage with fibroblastic proliferation. The arteries are normal.

*Prostate and Urethra:* At the periphery of the gland several small arteries show intimal thickening, which is due to a concentric deposition of dense lamellae of collagen. In the adventitia and less frequently in the media of these arteries there are groups of lymphocytes and plasma cells. A slight chronic inflammatory reaction is present in the mucosa of the urethra and the stroma of the prostate.

*Aorta:* The wall of the aorta is normal. In the adjacent fat tissue there are several small arteries with thickened intimal layers, narrow lumens and areas of lymphocytic infiltration in the adventitial connective tissue.

*Abdominal Lymph Node:* In the sinusoids numerous mononuclear phagocytes which contain red blood cells and hemosiderin are found. Eosinophiles are scattered through the gland. A small artery at the hilum shows concentric intimal hyperplasia, a narrow lumen and many small endothelial-lined channels in the thick fibrous adventitia.

*Bone Marrow:* The rib marrow contains an increased number of erythroblasts. A large amount of hemosiderin is demonstrable in large mononuclear phagocytes.

*Voluntary Muscle and Skin:* There are no lesions.

*Retina:* Between the outer and inner nuclear layers fibrinous thrombi occlude the lumens of several small capillaries. In two small areas necrosis and edema of the nerve fiber layer with hemorrhage into the retina and partial destruction of all layers internal to the pigment epithelium are found. The choroidal and retinal vessels are engorged, but no inflammatory lesions comparable to those in small arteries of other organs are detected.

*Brain:* Small areas of necrosis are numerous. These usually are characterized by hemorrhage and edema, some of which may be the result of operative trauma. However, several cortical and subcortical lesions show, in addition to hemorrhage and edema, a proliferation of glia cells, an infiltration with lymphocytes and monocytes and a proliferation of fibroblasts in the adventitia of small arteries. Acute thrombi are found in the lumens of occasional small vessels. A few lesions appear to be of several days duration. Other significant findings are occasional lymphocytes around small vessels in the medulla and pons and distinct small areas of myelin degeneration.

*Special Stains:* Numerous sections were stained by Wolbach's modification of the Giemsa stain and by the method of Gram-Weigert. These stains disclose no microörganisms that might be considered as etiological agents.

Sixty blocks of tissue from various organs were stained by Levaditi's method for the impregnation of spirochetes. In addition several blocks of cerebral tissue were treated by Jahnel's modification of the Levaditi and Manouélian method for the demonstration of *Treponema pallidum* in the brain and meninges. Only one section showed definite spirochetes although questionable forms appear in several sections. The spirochetes (Fig. 8) are located in the areas of necrosis and inflammation in the submucosa of the duodenum. They are morphologically consistent with *Treponema pallidum* and it seems justifiable to consider them as such.

*Anatomical Diagnoses:* Generalized syphilitic arteritis; multiple healed and acute arterial thrombi; acute and subacute infarcts of stomach, duodenum, ileum, colon, pancreas, liver, kidneys, adrenals, testes and brain; healed infarcts of pancreas, kidneys, adrenals and testes; localized acute and chronic peritonitis; bronchopneumonia; acute splenitis; chronic urethritis and prostatitis; fibrous perisplenitis and pleuritis; patent foramen ovale.

## Discussion

Instances of widespread inflammatory lesions of small arteries and arterioles have been observed and reported from time to time. Dickson [2] in 1908 reviewed the literature and added a case which he had studied. He discussed the lesions under two headings — Periarteritis Nodosa and Polyarteritis Acuta Nodosa. Opinion as to etiology has differed, but Dickson, along with others, believed that the former group was due to syphilitic infection and the latter group to some unknown infection or toxemia other than syphilis. Longcope [3] the same year presented a case of periarteritis nodosa with an excellent clinical and pathological review of the disease. He pointed out the much greater frequency among males than females. Mott, who wrote the section "Arterial Degenerations and Diseases" in Allbutt and Rolleston's System of Medicine,[4] agreed on the whole with Dickson as regards etiology and pathology. He discussed syphilitic disease of the small arteries and arterioles under the heading of Periarteritis Nodosa. This author emphasized the widespread distribution of the lesions, the frequent involvement of the coronary arteries and the early onset during the syphilitic infection. Allbutt[5] is quite in agreement with Mott.

Warthin [6] stated that syphilis involves the small arteries quite frequently. There is a large literature dealing with the effects of the syphilitic virus on the blood vessels, but practically all discussions are confined to observations on the cerebral and coronary vessels or the aorta and its larger branches.

When one consults modern text-books on pathology, such as those by Boyd [7] and MacCallum[8] little is to be found concerning the effects of syphilis on the small arteries and arterioles. Boyd does not believe that syphilis is the etiological agent in periarteritis nodosa. He uses as an argument the facts that periarteritis nodosa is chiefly a disease of the muscular type of arteries, while syphilis primarily attacks the elastic type.

Most authors agree that in syphilitic arteritis and in so-called periarteritis nodosa all coats of an artery may be involved. Opinions, however, differ as to the place of attack of the virus. The generally accepted explanation is that the lesion primarily occurs in the larger arteries about the vasa vasorum and in the smaller arteries in relation to the perivascular lymph channels.

The case presented here is of much interest from several points of view. The multiplicity, character and distribution of the symptoms, together with a hypertension of recent development, indicated that the patient had some disease of the vascular system. Longcope [3] pointed out that these findings, together with a leukocytosis and fever, would suggest the diagnosis of periarteritis nodosa, even in the absence of superficial vascular nodules. The fact that the patient had been quite well until he contracted his syphilitic infection, which was of recent occurrence, made it seem probable that his illness was due to this infection. Mott [4] and again Allbutt [5] noted that the widespread involvement of the small arteries by the syphilitic virus occurred early in the course of the infection; usually during the secondary stage, although not infrequently during the late primary stage, and that the whole course of the illness was usually from a few weeks to months in duration. These observations were borne out in our case.

The gross examination of the organs of this patient yielded no clue which would allow diagnoses other than those of disseminated arteritis and multiple infarcts. The assumption at the time of the postmortem was that idiopathic periarteritis nodosa was the malady which would explain all findings in the most satisfactory manner. It was only after microscopic study that the diagnosis of syphilitic arteritis was made. The histological study disclosed inflammatory changes in the walls of small arteries and in the periarterial tissues. There were a few vessels which were affected by a relatively acute inflammation. Most of the lesions were chronic or healed. It was impossible to determine what part of the vascular wall was the original site of the infection. It seemed that the outer portion of the media and the adjacent adventitia were affected primarily. Fibrosis of the vessel walls was prominent. The partial or complete occlusion of the lumens of the arteries by concentric thickening of the intima and thrombosis resulted in the formation of numerous infarcts.

Inasmuch as periarteritis nodosa has not been established as an entity and because the term has come to be used as an opportune "label" for most instances of arteritis of unknown etiology, it seemed that certain features of the present case favored a diagnosis of syphilitic arteritis rather than periarteritis nodosa. In the first place, the patient had contracted syphilis a few months before the

onset of his fatal illness. Secondly, the appearance of severe signs and symptoms occurred during the period in which generalized syphilitic arteritis is most likely to occur. Thirdly, although the patient was treated promptly with arsphenamine and mercury, the therapy was interrupted for several weeks before the onset of serious symptoms. This lapse of therapy would allow for an intense exacerbation of the disease such as, according to Moore,[9] not infrequently occurs in the central nervous system in instances of primary or early secondary syphilis under similar circumstances. Fourthly, the histology was more compatible with syphilis than any other disease. Fifthly, spirochetes, which were indistinguishable from the *Treponema pallidum*, were found in an area of necrosis in the submucosa of the duodenum.

Generalized syphilitic involvement of the small arteries must be uncommon. This is the first case of this type recognized in this hospital. It is impossible to state why the vascular system should have been so vulnerable to the virus. Stokes[10] states that both arsphenamine and mercury are toxic to the walls of blood vessels. In this case treatment was instituted early and was intensive over a period of several months. It may be that this is an example of the "therapeutic paradox" following the use of arsphenamine. Stokes[10] believes that this is due to the too rapid healing of the lesions. He states that "closure of a partially obliterated coronary vessel or branch by edema at some spot of active gummatous arteritis, as in the Herxheimer flare-up, or rapid strangulation by too quick scar formation and healing, may produce death before any compensatory mechanism can come into play." It is conceivable that some such occurrence took place in the present case. Another explanation which has been offered, especially in instances of neurorecurrences of which this is an example, is that early intensive treatment may have prevented the natural development of adequate bodily defences against the virus and that the lapse of treatment permitted a severe exacerbation of the disease.

## Summary and Conclusions

A case of widespread progressive chronic arteritis in a young adult with syphilis has been described. The small arteries were involved almost exclusively. All three coats of the vessels were in-

cluded frequently in the lesion. In most instances the vessels were occluded partially or completely, either by the marked thickening of their walls, by the formation of thrombi, or by a combination of the two processes. Infarcts of various organs often were present in regions where the most severe vascular lesions were found. The etiology of the arteritis has not been proved conclusively, but for several reasons cited in the discussion we believe it to be the virus of syphilis.

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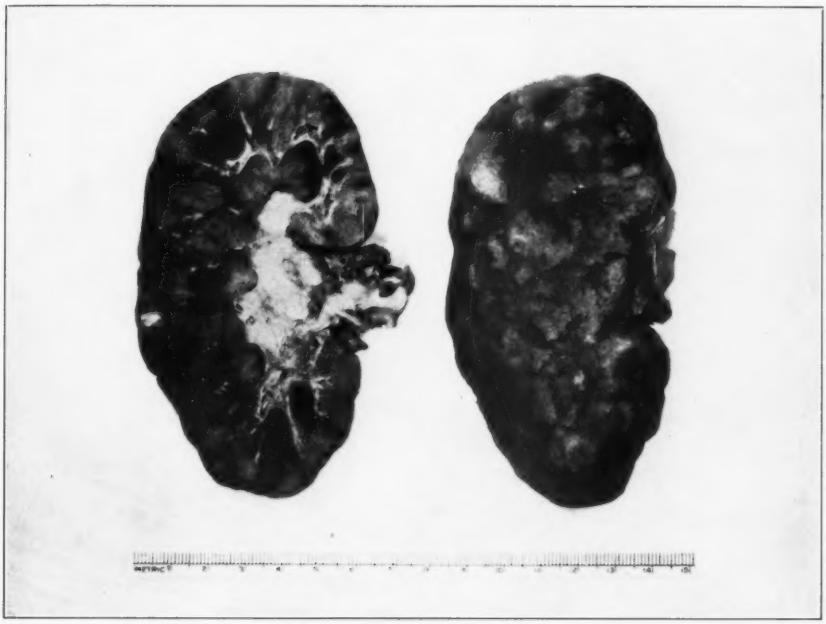
## DESCRIPTION OF PLATES

### PLATE 44

FIG. 1. Photograph of a coronal section of the kidney and of the external surface from which the capsule has been removed.

FIG. 2. Photograph of a distended segment of the ileum. Note the two areas of infarction.



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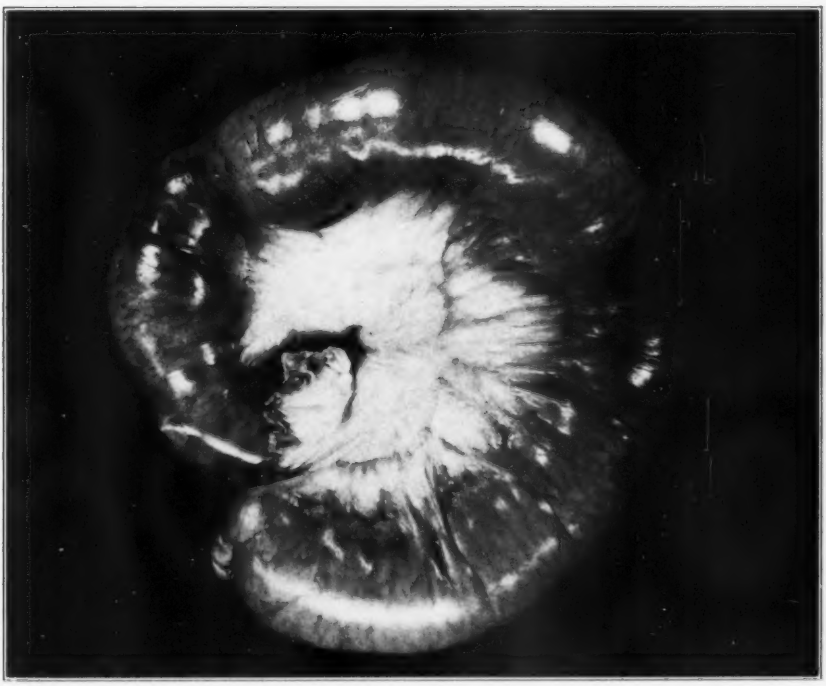


2

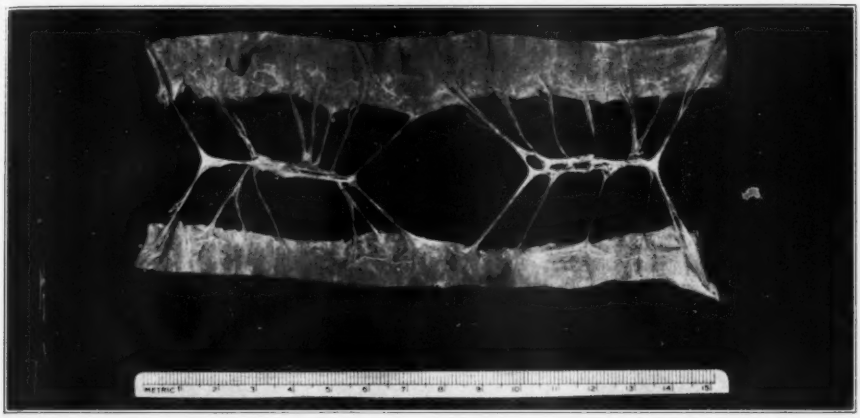
Derick and Hass Diffuse Arteritis of Syphilitic Origin

## PLATE 45

FIG. 3. The specimen for this photograph was prepared in the following manner. A segment of a normal ileum was selected. A dissection of the terminal arcuate branches of the superior mesenteric artery was made. The ileum was then bisected in the plane of the mesentery and the divided halves of the wall spread out so as to show the paired arcuate branches in one plane.

FIG. 4. The specimen for this photograph was selected from a portion of the ileum between the areas of infarction in the present case. It was prepared in the same manner as the normal ileum in Fig. 3. Note the increased opacity and thickness of parts of the arcuate arteries. This illustrates the scattered distribution of prominent lesions without true modosities or aneurysmal dilatations. The vessels from which these arteries arose were normal.

FIG. 5. Photomicrograph of a thickened terminal arcuate artery (such as those in Fig. 4) and an accompanying vein. Note the fibrosis, vascularization and cellular infiltration in the media and adventitia. This also exemplifies the typical intimal proliferation with consequent narrowing of the vascular channel. × 100.



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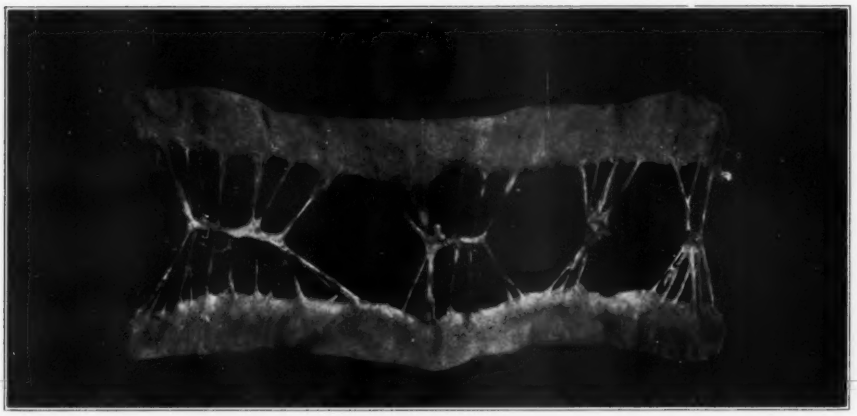

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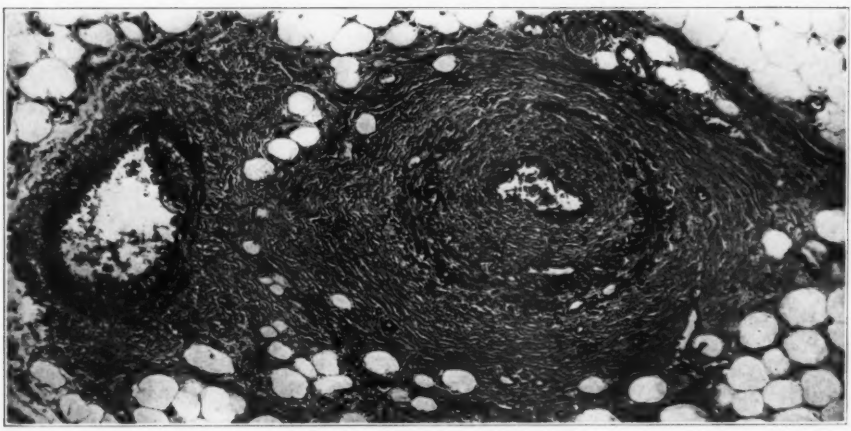


5

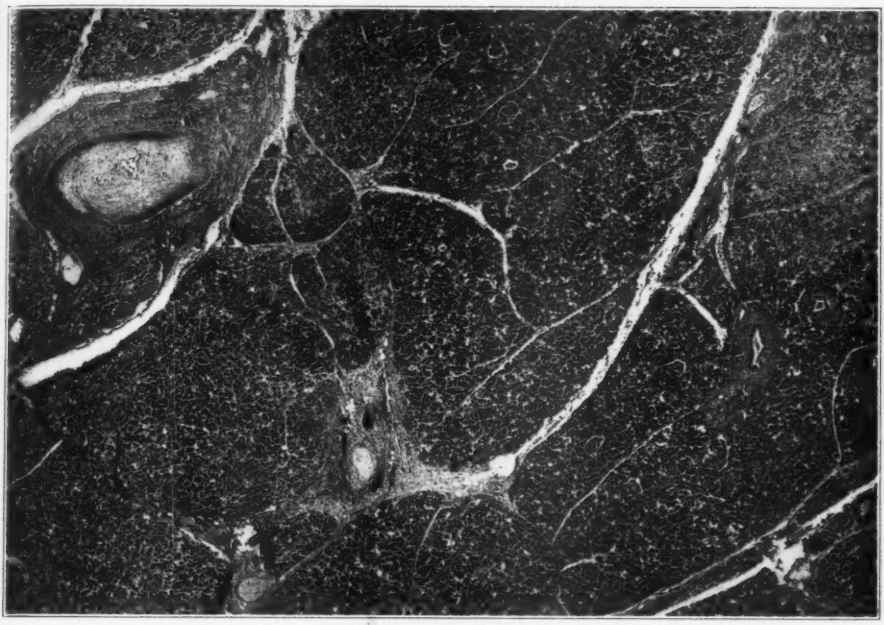
Derick and Hass Diffuse Arteritis of Syphilitic Origin

PLATE 46

FIG. 6. Photomicrograph of the pancreas. Note the extraordinary intimal proliferation in the large artery. The two small arteries are similar histologically to the arcuate artery in Fig. 5. A small area of parenchymal fibrosis is also included in the picture. × 25.

FIG. 7. Photomicrograph showing the type of lesion found in the large artery in Fig. 6. It illustrates the typical pathology of the largest vessels which were involved by the disease. × 100.

FIG. 8. Photomicrograph of one of the *Treponema pallidum* in the wall of the duodenum. × 2000.



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Derick and Hass

Diffuse Arteritis of Syphilitic Origin

# CONGENITAL ANOMALY OF THE HEART *

## REPORT OF A CASE, WITH EMBRYOLOGICAL DISCUSSION

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As far as the author is aware, such a combination of congenital anomalies of the heart as persistence and detorsion of the bulbus cordis, partial transposition of the aorta, interauricular and interventricular septal defects, patent ductus arteriosus, sinistroposition of the right auricle and right aortic arch has hitherto rarely been recorded in the medical literature. One of the cases (Case 9) reported by Wenner [1] seems to correspond fairly closely to such a description. This author, however, labelled it *cor monoventriculare biatriatum*, in spite of the presence of a low but thick interventricular septum on the anterior ventricular wall about two finger breadths above the apex. A case with this combination of anomalies, which was under observation for about 7 weeks in the pediatric service of the Peiping Union Medical College Hospital, presents a few anatomical features that seem to shed a new light on some of the aspects of our knowledge of the embryology of the heart. For these reasons a detailed report of the case with a discussion of the mechanism of its development seems warranted.

### REPORT OF CASE

*Clinical History:* S. H. M., a Chinese female infant, aged 53 days, was admitted to the pediatric service of the Peiping Union Medical College Hospital on Dec. 20, 1929, for frequent cough of more than 20 days duration. After birth the patient had been apparently normal, except for some edema of the legs, which practically disappeared in 10 days. Fifteen or 16 days after birth she began to have some nasal discharge and frequent cough. She cried often and had attacks of cyanosis, rapid and difficult respiration, perspiration, occasional vomiting and, later, unconsciousness. There had been no other complaints. She was born at term and spontaneously, and never had any illness, except as mentioned. The parents were healthy and denied venereal disease. The mother had had one other pregnancy, a girl 4 years of age, living and well.

On admission the important physical findings were as follows: temperature 37° C.; pulse rate 168 per minute; respiration rate 42 per minute, at times

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more rapid and labored; dark color of the skin; moderate cyanosis of the mucous membranes; slight enlargement of the cardiac dullness toward the left; aortic second sound slightly accentuated; a fairly loud, short, blowing systolic murmur over the whole precordium; slight dullness with diminished breath sounds over the anterior right upper region of the chest; medium moist râles over lower posterior portion of the chest on both sides, and definitely palpable liver edge 1.5 cm. below the costal margin.

After admission the patient was found to be excitable and had cyanosis and dyspnea during convulsions, which could be curtailed by the administration of chloroform or morphine. Typical "obstetrical hand" was noticed on one occasion only. Roentgenological examinations of the chest done on Dec. 21 and 31, 1929, and Jan. 13, 1930, revealed persistent opacity in the region of the right upper lobe of the lung, and the possibility of an azygos lobe was suggested. On January 8th an abscess of the left thigh was incised. On January 19th a furuncle of the right external auditory canal was noticed and treated.

During the patient's stay in the hospital her condition and physical findings, except as noted above, remained stationary. On February 5th she had another attack of cyanosis and dyspnea, for which morphine injection was given. She failed to recover and died, presumably of respiratory failure, after having lived 100 days.

The laboratory findings were as follows.

*Urine:* Acid in reaction, 1 plus albumin, occasionally positive sugar reaction, a few white blood cells and granular casts in sediment.

*Blood:* On admission red blood cell count 5.03 million per cmm., with 134 per cent hemoglobin value (Sahli). White blood cell count 6800 per cmm. with 53 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 45 per cent lymphocytes and 1 per cent monocytes.

On Feb. 2, 1930, the red blood cell count was 4.2 million per cmm., with 89 per cent hemoglobin value (Sahli).

*Feces:* No protozoa or ova.

*Clinical Diagnoses:* Congenital malformation of the heart; questionable patent ductus arteriosus; bronchopneumonia, left lower lobe, microörganism undetermined; atelectasis, right upper lung; otitis externa.

## Autopsy Report

The autopsy was done approximately 21 hours after death. The body was that of a well developed but poorly nourished, Chinese female infant weighing 3 Kg. and measuring 54 cm. in length. Rigor mortis was moderate and livor mortis was present over the dependent portions. The skin was dark colored, the mucous membranes definitely purplish. The skull was of normal contour; the anterior fontanelle was open, 1.5 by 1.2 cm., the posterior fontanelle closed. A small amount of thin yellowish discharge was present in the right auditory canal. Eyes and nose were normal. The abdo-

men was slightly distended. Extremities showed no clubbing of fingers or toes and no other abnormal findings. The external genitalia were normal.

The peritoneal cavity contained a small amount of clear yellowish fluid; the surfaces were smooth and glistening. The omentum was free in the cavity. The intestines were moderately distended with gas. The liver and spleen were in their normal positions.

The right and left pleural cavities contained no excess of fluid and their surfaces were smooth and glistening. The lungs were voluminous. The pericardial sac contained a few cc. of clear yellowish fluid. The heart was much enlarged and, as its exposure revealed an apparent malformation, the body was immediately embalmed so as to allow a careful dissection of all the larger blood vessels. The thoracic and abdominal organs were removed *in toto*.

The heart was much enlarged and was approximately three times the normal size of that of a 3 months old infant. Its shape was like that of a pear, with the anteroposterior diameter longer than the transverse, being 4 and 3.5 cm. respectively. The greatest circumference around the ventricles was 12.4 cm. and the vertical length from the level of the origin of the aorta to the inferior border was 5.2 cm. From the sternocostal surface (Fig. 1), the most striking abnormality was the position of the aorta. It arose from the extreme right upper conus of the heart directly anterior to the origin of the pulmonary arterial trunk. On the left side there lay both the right and the left auricular appendages, the former being the more cephalic of the two. The apex was globular and formed entirely by the left ventricle. The diaphragmatic surface (Fig. 2) showed that a greater part of the upper portion was occupied by the left and right auricles, into which their respective veins entered, and a smaller part was occupied by the arterial trunks at the extreme upper right portion. The lower portion of this surface is the ventricular area. Between the sternocostal and the diaphragmatic surfaces was the acute margin (Fig. 3), which was by no means distinct and on which the marginal branch of the circumflex artery ran. The left surface of the heart, or the obtuse margin, was broad and showed the origin of the aorta from the ventral and cephalic ventricular portion, the pulmonary arterial trunk being hidden. The right and left auricular appendages were clearly shown to lie in apposition to each other.

The aorta, after its origin from the right ventricle, where it measured 1.3 cm. in diameter, ran cephalad and dorsad, and was ventral and to the left of the pulmonary arterial trunk. It gave off the left innominate, the right carotid and the right subclavian arteries in the order named, about 2.5 cm. from the level of its origin. The aorta communicated with the right branch of the pulmonary artery by a patent ductus arteriosus, which measured 4 mm. in length and barely admitted a probe, so that the diameter of its lumen was not more than 1.5 mm. At this level the aorta arched over the right bronchus and was continuous with the thoracic and abdominal portions of the aorta, which were normal.

The pulmonary arterial trunk also took its origin directly dorsal to the aortic orifice, and measured about 1.4 cm. in diameter at this level. It closely followed the course of the aortic arch and remained dorsally and on the right. At the level where the left innominate artery arose from the aorta, the pulmonary arterial trunk branched. The right branch, after giving off the ductus arteriosus, ran dorsad and toward the right to the hilum of the right lung, while the left passed caudad to the transverse aorta and reached the hilum of the left lung. Both of these arteries were moderately dilated.

Because of the malformation, it was not practicable to open the heart by the usual technique of following the blood stream. Thus, the pulmonary veins and the left auricle were opened first. It was noted that the auricle was apparently normal, being lined by smooth and glistening endothelium with its usual pectinate muscles in the appendage. The interauricular septum was found to be normal in appearance, but the foramen ovale was patent, measuring 8 by 4 mm. There was no trace of the foramen primum. When one looked into the left ventricle the mitral orifice appeared to be irregularly oval in shape and was 11 and 7 mm. in diameter. The ventricular wall was then cut between the two normal papillary muscles, to which were attached by normal chordae tendineae a large anterior and a small posterior cusp of the mitral valve. As the left ventricle was thus exposed, the interventricular septum appeared normal (Fig. 4), but when the anterior leaflet of the mitral valve was elevated a septal defect measuring 9 by 5 mm. was present at its cephalic end. It was roughly U-shaped with a smooth and rounded edge. The height of the left ventricular surface of the interventricu-

lar septum measured 19 mm. The left ventricle communicated with the left auricle through the mitral orifice and with the right ventricle through the septal defect. No efferent vessel was derived from it. The left ventricular wall measured 11 mm. in thickness.

The right auricle was then exposed, showing no abnormal findings other than the defect in the interauricular septum above described. The tricuspid orifice was sickle-shaped, measuring about 15 mm. in length. An oblique cut was then made on the right ventricular wall. The arterial trunks were cut open longitudinally and the incisions extended to the right ventricular wall until they met. In such a way, a V-shaped portion of the ventricular wall could be lifted up, exposing the right ventricular cavity (Fig. 5). This was found to be smaller than the left ventricle and was cephalad, ventral and to the right of it. The thickness of the right ventricular wall measured 9 mm. The tricuspid cusps were normal and were provided with normal chordae tendineae and three short but plump, papillary muscles.

The right ventricle communicated with the right auricle through the tricuspid orifice, with the left ventricle through the interventricular septal defect, and with the aorta and the pulmonary arterial trunk through their respective orifices. It was bounded on all sides by a rather thick muscular wall, the shape of which resembled the bulbus cordis in the heart of an early embryo. Caudad, it was separated from the left ventricle by the defective interventricular septum. Between the aortic and the pulmonary orifices and extending into the cavity there was a thin fleshy flap, the bulbar septum (Fig. 5), which measured from 7 to 11 mm. in height.

The aortic orifice was guarded by three normal appearing semilunar cusps (Fig. 8, *b*), one anterior, one right posterior and one left posterior. From the right posterior sinus of Valsalva there arose the right coronary artery. A shallow dimpling was present on the aortic wall in the left posterior sinus of Valsalva, representing the rudimentary left coronary artery.

The orifice of the pulmonary arterial trunk was also guarded by three normal semilunar cusps, one posterior, one right anterior and one left anterior. The aperture of this trunk was slightly larger than that of the aorta.

After suturing some of the cuts above mentioned, the heart was then divided into two halves by extending the cut in the left ventric-

ular wall so that each half carried one arterial trunk (Fig. 6). In such a way a remarkable picture was produced. It was noted that the right ventricle, from which the two arterial trunks arose, was composed of a conically shaped muscular tube corresponding in shape and position to the bulbus cordis of an early embryonic heart. The orifices of the arterial trunks were at a much higher level than the auriculoventricular orifices. The interventricular septum took its origin from the ventral surface at a level between the middle and lower thirds. It was placed in such a plane that the right ventricular surface pointed cephalad, slightly ventral and to the right, while the left ventricular surface faced caudad, slightly dorsal and to the left. Its free margin was directed toward the caudal end of the interauricular septum, but was separated from it by the interventricular foramen. The left ventricle was thus at a lower plane than, or caudad to, the right. The tricuspid and mitral orifices were approximately at right angles to the interventricular septum.

The right coronary artery (Fig. 7), after taking its origin from the right posterior aspect of the aorta, emerged between the two arterial trunks and ran laterally to the right for a short distance. Then it branched into two, one circumflex and one infundibular branch. The former traveled posteriorly and toward the left in the coronary sulcus and gave off (1) a marginal branch at the level of the right border of the pulmonary trunk running along the acute margin; (2) a posterior descending ramus, which ran downward over the posterior surface, its branches terminating over the lower border of the sternocostal surface; (3) a number of posterior rami on the left ventricle supplying the left ventricular wall; and (4) a terminal branch which ended over the left surface of the heart. The infundibular branch ran obliquely anteriorly and soon gave off (1) an anterior ramus, which ran obliquely downward and slightly to the left at the right border of the heart, terminating at about the lower fourth of the anterior surface; and (2) an anterior descending ramus, which wound transversely around the infundibulum of the aortic trunk and reached the border of the right auricular appendage, where it turned sharply so that it ran obliquely downward and slightly toward the right, terminating at a point 1.8 cm. from both the right and the inferior borders of the heart on the anterior surface.

The right lung was three lobed, but an extra fissure was present over the lower lobe and over the posterior surface of the upper lobe.

The latter corresponded to the sulcus usually formed when an azygos lobe of the lung exists. Although at time of autopsy the presence of an azygos vein was unfortunately not definitely ascertained, the clinical and pathological pictures fit in well with such a condition. The left lung consisted of one lobe; however, a few shallow fissures were present over the surface. The pleural surface was smooth and glistening. The consistence was soft and crepitant, except in the right upper region where it was slightly firm. On section the cut surface showed atelectasis of the azygos lobe. The bronchi and the bronchial lymph nodes were normal.

The other organs showed no noteworthy findings.

As a whole, the microscopic study of different organs was not remarkable. The section of the heart showed normal myocardium. The sections of the lungs showed a moderate degree of emphysema in all the lobes, except the right upper lobe where a partial atelectasis and some leukocytic exudate in a few alveoli were present.

*Anatomical Diagnoses:* Congenital anomaly of the heart with persistence and detorsion of bulbus cordis, partial transposition of the aorta, interauricular and interventricular septal defects, patent ductus arteriosus, sinistroposition of the right auricle and right aortic arch; hypertrophy of the heart; anomaly of the coronary arteries; partial atelectasis and lobular pneumonia of azygos lobe of the lung; anomaly of the lung (single lobe of left lung with fissures, small fissures in the right lower lobe).

## Discussion

In his study on the development of the human heart from its first appearance to the stage found in embryos with twenty paired somites (1.5 to 3.3 mm.), Davis [2] reports that the embryonic heart is composed of aortic-bulbar, cardiac-bulbar, ventricular and atrial regions, demarcated by the interbulbar, bulboventricular and atrioventricular sulci ectally, and their corresponding ridges entally. With the growth of the cardiac tube much exceeding that of the pleuropericardial sac, and with the difference in the rate of growth in different regions of the heart, there occurs a bending of the cardiac tube, forming an S-shaped structure and a shifting in the positions and a change in the relative exaggeration or obliteration of the different sulci and ridges. In all of the embryos that he studied, these landmarks are definitely present.

In almost all the standard text-books of human embryology it is noted that in the embryo of about 5 mm. a definite sulcus appears at the bottom of the common ventricle, marking out the future right and left ventricles, and another slightly less definite one on the right side between the bulbus and the right ventricle. In the embryo of about 10 mm. the rudimentary interventricular septum appears between the dilated right and left ventricles, with a corresponding ectal interventricular sulcus. Another shallow ectal sulcus (the right bulboventricular) and a corresponding low ental ridge or spur persist between the bulbus and the right ventricle. In the embryo of about 15 mm. the interventricular septum is set vertically on the floor of the common ventricle and directed toward the auriculoventricular endocardial cushions, thus incompletely dividing the common ventricle into two chambers. With further development of the right ventricle, the right bulboventricular ridge becomes obliterated.

The bulbus cordis is only a transient, but important, structure in the development of the human heart. It soon becomes incorporated with the right and the left ventricles, mostly the former, and forms the infundibular portions.

In the above review there are a few points that seem to be rather confusing. The value of definite landmarks in the interpretation of morphological development has been demonstrated in the works of Schulte,[3] Murray[4] and Yoshinaga[5] in the development of the mammalian heart. It is definitely shown by Davis[2] that there exists an interbulbar sulcus and ridge in the heart of embryos at, or before, the stage of twenty paired somites. This landmark is neither represented nor mentioned in the studies of the hearts of embryos of 5 mm. or more. What becomes, then, of this sulcus and ridge in the heart of these embryos? The interventricular sulcus, which denotes the origin of the interventricular septum, appears in the hearts of embryos of 5 mm. or more, but where is this sulcus in the hearts of embryos at, or before, the stage of twenty paired somites? Unless one assumes that the interventricular sulcus does not appear in the hearts of embryos before, and the interbulbar sulcus becomes entirely obliterated in the hearts of those after, the twenty paired somites stage, both of which are not likely to be the case, this discrepancy is not conceivable.

In the case reported here it is noted that the right ventricle con-

sists of a thick, muscular, tubular structure corresponding in position and shape to the bulbus cordis of an early embryonic heart. The interventricular septum arises from the ventral wall at a level corresponding to that of the bulboventricular ridge in the hearts of embryos of from 2 to 3 mm., runs obliquely and slightly cephalad, and fuses with the auriculoventricular endocardial cushions. It is also noted that the orifices of the arterial trunks are at a much higher level than the auriculoventricular ones, corresponding to the situation existing in a heart of an early embryo. Such a remarkable picture cannot be rationally explained by our text-book knowledge of the development of the heart, unless one assumes that the interventricular septum is malposed.

To clarify the confusing points, as noted above, one should scrutinize closely the difference in the interpretations of these observations. From his beautiful preparations, Davis [2] is justified in dividing the bulbus cordis into the aortic and cardiac portions, which are demarcated by the interbulbar sulcus ectally. The bulboventricular sulcus is a definite and important landmark, as will be discussed presently. On account of the simultaneous growth of the cardiac bulbus and the ventricular loop, which produces a downward displacement of the cardiac bulbus, the right bulboventricular sulcus shifts and appears at the bottom of the so-called "common ventricle" and is called by the older writers the interventricular sulcus. At the same time, the descent of the bulbus brings down the interbulbar sulcus, which has been erroneously considered as the bulboventricular sulcus. It seems reasonable, therefore, to consider that the bulboventricular sulcus of Davis and the interventricular sulcus are one and the same, and the interbulbar sulcus and the bulboventricular sulcus described in the text-books are also one and the same landmark. The interventricular septum is, therefore, developed from the right bulboventricular ridge of Davis.* With this change in the interpretations of these landmarks, it will follow that the ventricular loop of the early embryonic heart is destined to form the left ventricle, the cardiac bulbus the right ventricle of the adult heart, and that the aortic bulbus, by virtue of its torsion, the infundibular portions of both the right and the left ventricles.

* In this connection, Murray [4] claims that the left bulboventricular ridge contributes to the formation of the interventricular septum of the adult heart of the rabbit.

Keeping this in mind, the findings in our case can be easily explained by an inhibition in growth and a lack of downward displacement of the cardiac bulbus, so that the interventricular septum remains in a position corresponding to that of the bulboventricular ridge of an early embryonic heart and the orifices of the arterial trunks maintain a higher level than the auriculoventricular orifices. Similarly, the case of *cor biatriatum triloculare*, reported by Holmes [6] and republished by Abbott,[7] in which a defective septum appears between the so-called "common ventricle" and a small cavity from which the pulmonary artery is derived, can be explained by the assumption that this septum represents the normal interventricular one, arises from the bulboventricular ridge, but appears to be "malposed" on account of an atrophy of the cardiac bulbus, and a hypertrophy and marked dilatation of the left ventricle.

In explaining most of the anomalies of the bulbus cordis it is a distinct advantage to separate the aortic and the cardiac portions of the bulbus, as a disturbance in one may not necessarily affect the normal development of the other.

Because of the lack of descent of the aortic bulbus in our case, the partial transposition of the aorta, *i.e.* both arterial trunks arising from the right ventricle, is naturally to be expected. In view of the recent work on the torsions of the bulbus cordis (*i.e.* the aortic bulbus) the anterior or ventral position of the aorta in relation to the pulmonary trunk can readily be explained on the detorsion basis. In order to get to the normal heart, the distal end of the aortic bulbus will have to make a clockwise rotation, or torsion, of about 180°. In the present case, as illustrated in Figure 8, the torsion stops at approximately 60°, hence the detorsion defect.

The final closure of the interventricular septal defect is normally made by the bulbar septum, which forms the membranous portion. This septum in the present case is well formed, but on account of the lack of descent of the cardiac bulbus and of complete torsion of the aortic bulbus, it is unable to close the interventricular foramen.

The sinistroposition of the right auricle closely resembles the case of Birmingham [8] and that of Wenner.[1] The latter author has demonstrated clearly in his paper that this is due to the malposition of the aortic bulbus ("truncus arteriosus," according to this author). Normally, the aortic bulbus should ascend upward and toward the

left, passing in between and ventral to the right and left atrial pouches, but in these abnormal cases it passes directly upward on the right side of the right atrial pouch. It is conceivable that this malposition of the right auricle may have some inhibitory effect on the normal development of the right ventricle.

The right aortic arch is well discussed by many authors and it is sufficient here to explain it by the persistence of the right instead of the left fourth arterial arch. The left fourth arch instead of the right becomes the left innominate artery, and the persistent right sixth arch instead of the left the ductus arteriosus.

Anomalies of the coronary arteries are not rare. In the case here reported, the right coronary artery took its origin from the right posterior sinus of Valsalva, which usually gives rise to the left branch, but on account of the incomplete torsion of the aortic bulbus the left coronary artery became the right one. Because of the arrest in growth and absence of the other coronary artery the infundibular branch of the right one became compensatorily dilated.

Clinically there are remarkably few physical signs in this case, except a definite, loud, short, blowing systolic murmur heard over the precordium, and cyanosis and dyspnea during convulsions.

The intracardiac circulation of blood in this case (Fig. 9) undoubtedly involves a free mixing of the arterial and venous blood before it is sent out into the systemic bed. In a resting state of the patient cyanosis does not occur, probably because of the insufficient oxygen-unsaturation of the peripheral blood, or of the high "threshold value" in this particular case on account of its dark coloration of the skin. However, when the oxygen-unsaturation is raised above this "threshold value," as during convulsions, cyanosis occurs. The finding of partial atelectasis and pneumonia in the azygos lobe of the lung may contribute in a slight degree to the production of cyanosis in this case. Thus, in the terms of Lundsgaard and Van Slyke,[9] the cyanosis in our patient is mainly produced by the $a$ and D factors, and slightly by the $l$-factor.

## Summary and Conclusions

An unusually rare case of congenital anomaly of the heart with persistence and detorsion of the bulbus cordis, partial transposition of the aorta, septal defects, patent ductus arteriosus, sinistroposi-

tion of the right auricle and right aortic arch is described in detail. Anomalies of the coronary arteries and of the lung are also noted.

It is suggested that the interventricular septum develops from the bulboventricular ridge of the early embryonic heart. With the arrest of growth of the cardiac bulbus resulting in a lack of downward displacement of the right ventricle, which is developed from the cardiac bulbus, and a lack of descent and detorsion of the aortic bulbus, the almost horizontal position of the interventricular septum, the high level of the orifices of the arterial trunks and the conical shape of the right ventricles are explained.

Clinically, there are remarkably few physical signs, so that an exact ante mortem recognition of this condition is almost impossible. Cyanosis occurs only during physical exertion.

NOTE: The author wishes to acknowledge his indebtedness to Dr. I. C. Wen, of the Department of Anatomy, and Dr. C. E. Forkner, of the Department of Medicine, Peiping Union Medical College, Peiping, China, for valuable criticisms in the preparation of this paper.

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## KEY TO THE PLATES

A O = Aorta
B S = Bulbar septum
D A = Ductus arteriosus
D I = Diaphragmatic surface
F O = Foramen ovale
I C = Inferior vena cava
L A = Left auricle
L I = Left innominate artery
L P = Left pulmonary artery
L V = Left ventricle
M A = Acute margin
M O = Obtuse margin
M V = Mitral valve
P A = Pulmonary artery
P V = Pulmonary vein
R A = Right auricle
R C = Right carotid artery
R S = Right subclavian artery
R V = Right ventricle
S I = Septum primum
S II = Septum secundum
S C = Superior vena cava
S C = Sternocostal surface (in Fig. 7 only)
T O = Tricuspid orifice
T V = Tricuspid valve
V S = Interventricular septum

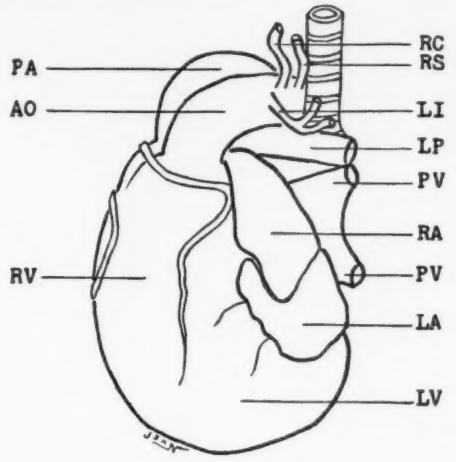
## DESCRIPTION OF PLATES

### PLATE 47

FIG. 1. Sternocostal surface showing origin, position and course of aorta in relation to pulmonary artery and trachea, the sinistroposition of the right auricle and the general shape of the heart.

FIG. 2. Diaphragmatic surface.

FIG. 3. Acute margin.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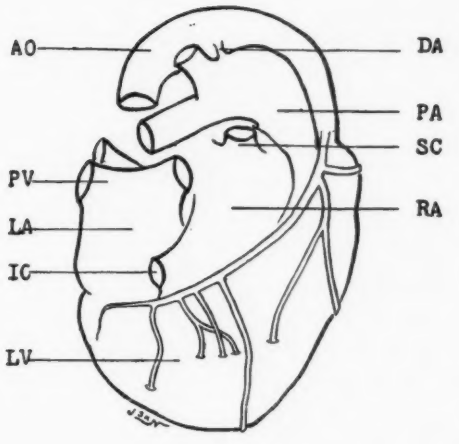
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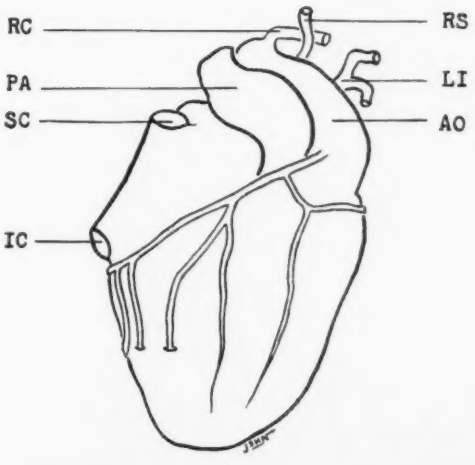
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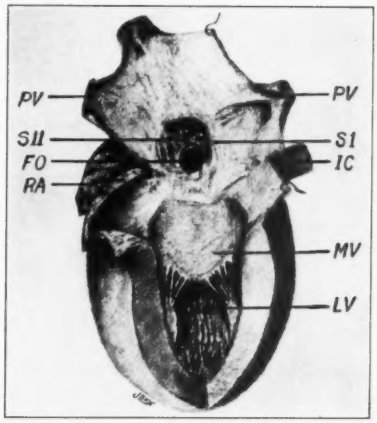
## Plate 48

Fig. 4. Showing interior of left auricle and left ventricle.

Fig. 5. Showing the left and right ventricle, the interventricular septum with its defect and the origin of the arterial trunks from the right ventricle.

Fig. 6. Showing the interior of the heart.

1 = Pulmonary artery
2 = Aorta
3 = Right ventricle
4 = Left ventricle
5 = Right auricle
6 = Left auricle
7 = Bulbar septum
8 = Interoventricular septum
9 = Papillary muscle to mitral valve
10 = Interauricular septum
11 = Pulmonary vein

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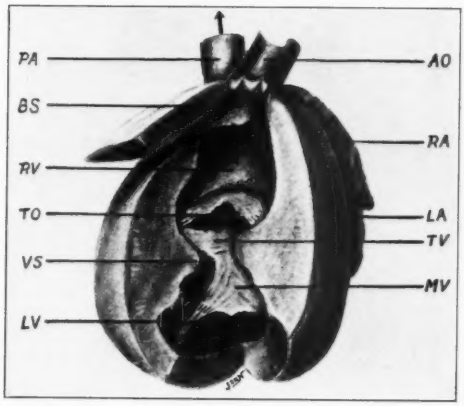


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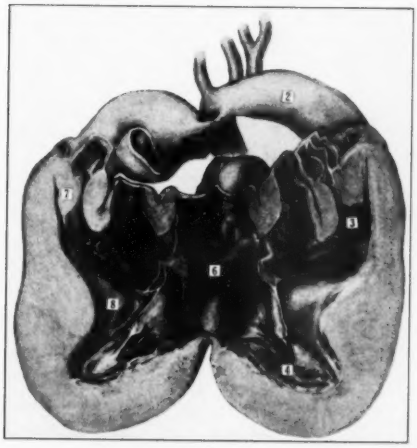

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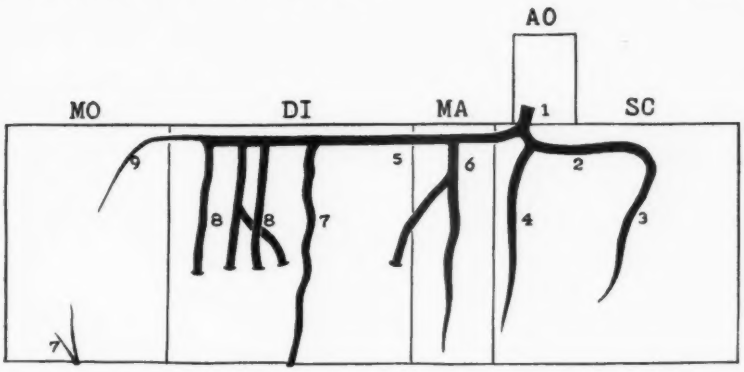
## Plate 49

Fig. 7. Diagrammatic representation of the distribution of the ventricular branches of the coronary artery.

1 = Right coronary artery
2 = Infundibular branch
3 = Anterior descending ramus
4 = Anterior ramus
5 = Circumflex branch
6 = Marginal branch
7 = Posterior descending ramus
8 = Posterior rami of left ventricle
9 = Terminal branch of circumflex

Fig. 8. (A) = Position of aortic *A*, and pulmonary *P*, orifices in heart of early embryo.
(B) = Position of *A* and *P* in heart of author's case.
(C) = Position of *A* and *P* in heart of normal person.

Fig. 9. Diagrammatic representation of intracardiac circulation of blood.

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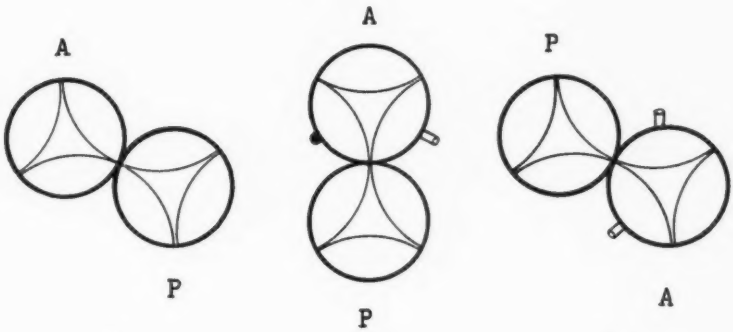


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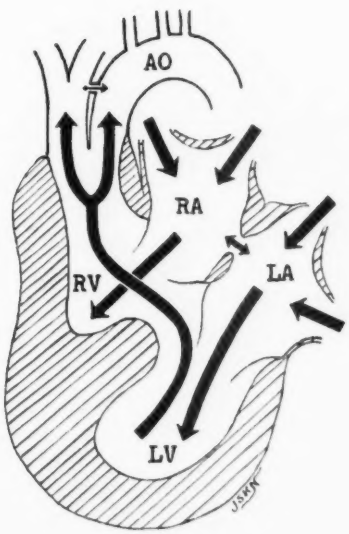


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# SACROCOCCYGEAL TERATOMA *

## REPORT OF A CASE

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Sacrococcygeal teratomas are reported in the literature at regular intervals. The histological characteristics determining the nature of this tumor are definite, but the exact embryological origin is still a matter not entirely clear. We present here the study of one such case that came to autopsy in the Buffalo City Hospital.

## REPORT OF CASE

*Clinical History:* On Oct. 26, 1932, a Polish female entered the Buffalo City Hospital in the first stage of labor. In her 29 months of married life she had given birth to one normal child. There were no miscarriages. The last menstrual period began on March 29, 1932. In the latter part of pregnancy "multiple fetal parts" were noted and a diagnosis of twin pregnancy was made. The patient was one of twins and has two other twin sisters. This is of special interest when one considers the bigerminal theory of origin of teratomas. Labor lasted 18 hours and the fetus with a large sacral tumor was born dead.

## AUTOPSY PROTOCOL

The autopsy was performed 27 hours after birth of the infant. The body was that of a white female infant weighing 6 pounds and measuring 34 cm. from vertex to coccyx, and 48 cm. total length. There was pitting edema of both lower extremities.

A large, globular, somewhat pear-shaped tumor mass was present over the buttocks, extending into the perineum posterior to the anal orifice (Figs. 1 and 2). This mass measured 9 by 12 cm. in its greatest diameter. On mesial section it was noted that a narrow portion near the rectal triangle was 2 cm. in diameter. The consistence of the tumor was firm and it was covered by skin which, at the upper extremity, was very thin. On section the tumor was soft, gray, friable, gelatinous and brain-like, with areas of hemorrhage. Many cystic clefts were scattered over the cut surface, some of which contained a clear straw-colored fluid. Strands of white fibrous

* Received for publication August 25, 1934.

tissue coursed irregularly over the cut surface and small, irregular, calcified fragments were encountered on sectioning. The tumor mass was found to fuse, by means of an isthmus, with a second cystic tumor mass occupying the true pelvis. This latter tumor measured 3.5 cm. in diameter and was firmly amalgamated with the rectum anteriorly, while posteriorly its capsule was loosely blended with the presacral fascia. The connection between the two masses was more like a compressed portion of one tumor, the pelvic portion compressing the rectum, vagina and urethra. The fundus uteri was elevated above the pelvic brim and the ureters, sigmoid colon and rectum were displaced anteriorly, while posteriorly the iliac veins were compressed. Definite organ rudiments or distinctive tissue elements could not be recognized in the tumor.

The peritoneal cavity contained 20 cc. of clear, straw-colored fluid. The heart was not remarkable. The lungs were atelectatic. The splenic capsule was fibrously thickened. The renal pelves were dilated and thin-walled.

## Microscopic Examination

Numerous tissue blocks were made from various parts of the tumor. These were embedded in paraffin and sections stained by the hematoxylin-eosin, Unna orcein, Van Giesen, scharlach R, Spielmeyer, Holzer, and Bielschowski methods.

Tissue representatives from all three primary germ layers were recognized in the form of definite nests of squamous-celled epithelium, fibrous connective tissue, bundles of smooth muscle, cartilage, mucus-secreting, cuboidal-columnar cells arranged in small alveoli, transitional epithelium, adipose tissue and osteoid matrix. In one section an island of cartilage yielded gradually by metaplasia to fibrous connective tissue. A partly calcified osteoid matrix in another section exhibited a central reticulated area containing large, thin-walled capillaries, with small concentrations of erythropoietic cells, *i.e.* immature megaloblasts, erythroblasts and macronormocytes.

The many cysts were of varying shape and size. Their lining cells were of two types. In the larger cysts they were small, round or cuboidal, with scant cytoplasm and nuclei which were stained deeply with hematoxylin; these cells were disposed mostly in two

and sometimes three layers, the deeper ones being smaller and less differentiated. There were many papillary projections of the cellular linings. In cross-sections of the villous processes the investing cells were cylindrical or somewhat fusiform, with a single nucleus situated at their basal poles. Thin-walled, blood-containing capillaries were in intimate contact with their centripetal ends, and a fine fibrous connective tissue reticulum formed their supporting stalk. This picture was suggestive of ependyma and choroid plexus. The other type of cyst was smaller, did not have papillary processes and its cells were palisaded in layers, with clearer, lighter staining nuclei containing several nucleoli, and their cytoplasm was more abundant and irregular. The stroma around these cystic areas was a loosely meshed, eosinophilic, fine fibrillar net. This at times was quite a prominent element in many sections. The cells enmeshed in the network were of two types; one had a round, deeply staining nucleus, while the other possessed an ovoid, larger and relatively clear nucleus with a dark nucleolus. The Bielschowski stain revealed some fibrils with intimately incorporated fine brown granules. At times these cells exhibited one or two, short, conical cytoplasmic processes and in a general way suggested glia cells.

Somewhat similar cells with little cytoplasm and a large, ovoid clear nucleus with a large, eccentrically placed nucleolus were seen in another section of the tumor. In the Bielschowski silver impregnated sections some of these showed a black, single, axon-like process, and at the other pole three or four finer dendritic processes suggesting sympathetic ganglia.

The sections through the tumor mass at the point of its attachment to the rectum revealed a defect involving all the muscular layers. A fibrous connective tissue filled this defect, extending apparently from the muscularis mucosae, merging gradually into the pelvic tumor described above.

The presence of derivatives from all three germinal layers classifies this tumor as a teratoma.

## Discussion

Sacrococcygeal teratomas are fairly well known. Pandalai, Forsyth and Stewart [1] in 1924 reported an intrapelvic teratoma in a 12 months old infant. The tumor had extended beneath the right

gluteus maximus. The dominant tissue elements were those resembling glia and choroid plexus.

Stewart, Alter and Craig [2] reported a sacrococcygeal teratoma in an infant aged 2 years and 11 months. This had become carcinomatous and had metastasized to the liver, lungs and inguinal lymph nodes. Sawday [3] reported a postrectal teratoma in a 4 year old child. This was removed surgically and the child died a uremic death within 1 month.

Keen and Coplin [4] in 1906 reported a sacrococcygeal teratoma in a 2 year old child. This tumor had an opening entirely through the sacrum, and communicating with this and the rectum there was a sinus which somewhat resembled a bronchus in structure.

Rosenbaum [5] reported the successful removal of a teratoma weighing 2 pounds from a 18 day old infant. This tumor apparently originated in the sacrococcygeal region. Leopold and Phillips [6] briefly described a retrorectal teratoma in 1906.

Davis [7] reported the case of a newborn infant with a pelvic teratoma that had invaded the perineum.

Parin [8] collected 16 reported cases which were considered to be congenital presacral tumors. These were reported between the years 1900 and 1909. Fifteen of them would definitely appear to be teratomas in relation to the rectum, sacrum or coccyx. He also cited 6 reported cases which were interpreted to have undergone malignant transformation with metastases.

Thompson [9] reported the successful removal of an intra- and extracoccygeal tumor the size of a cocoanut from a 6 months old infant, with no recurrence at the end of 2 years.

Hansmann [10] has reported a teratoma anterior to the sacrum in a newborn infant which, with 15 collected reported cases, he thought originated from the neurenteric canal. Hansmann and Berne,[11] in describing an additional case in 1932, tabulated the salient features of 25 retrorectal sacrococcygeal teratomas. These had been reported by various authors from 1924 to 1930. One, after surgical removal from a 31 year old female, recurred with metastases.

## Incidence

Infants born with pelvic teratomas are considered monstrosities. According to Marchand [12] (quoted by Keibel and Mall), 615 mon-

sters were found in 81,817 births. The percentage of sacrococcygeal teratomas was not stated.

Calbet [13] found sacral tumors (all varieties) to occur once in 34,582 births. Galletly[14] stated that Kiderlen in 1889 collected 122 cases of completely or partially presacral congenital teratomas from the literature.

In the Buffalo City Hospital from 1921 to 1933 there were 5424 births, 8 of which were monstrosities. Only 1 teratoma is recorded.

Ewing [15] writes that one-third of fetuses with sacrococcygeal teratoid tumors are born dead, and 90 per cent of the others die soon after birth.

## Theories of Origin

The various theories regarding the origin of these tumors include:

(*A*) Adami's [16] theory of continued growth of totipotential cells at the inferior growing point.

(*B*) The unrelated individual development of a blastomere which has been isolated during segmentation of the ovum.

In regard to theory (*B*) Hansmann and Berne stated that disorderly growth of tissue in the presacral region occurs later in fetal life and, therefore, is a more likely cause.

(*C*) The extrusion of an impregnated polar body.

(*D*) Herrmann and Tourneux [17] thought that nerve tissue was derived from a persistence of the medullary coccygeal vestige and that ependyma and neuroglia proliferation could give rise to cystic and adenomatous growths.

(*E*) Bonney's [18] theory of inferior dichotomy of the fetal axis.

Bucy and Haymond,[19] in reporting a lumbosacral teratoma associated with spina bifida, thought that it was a "twin," whose development had been partially inhibited, assuming that a "division of the ovum might have occurred at any time during the presence of the primitive streak, *i.e.* up to the fourth week following fertilization."

(*F*) Borst [20] thought that coccygeal remnants might be transplanted to the ventral side of the sacrum and give rise to teratomas.

(*G*) The theory of *fetus inclusio fetalis* has been referred to as the cause of sacrococcygeal teratoma by Hirst and Piersol,[21] McFarland,[22] Payne,[23] Cutler,[24] and Williams.[25] In regard to bigerminal

(*fetus inclusio fetalis*) and monogerminal origin, Ziegler[26] makes the following anatomical distinction: "If a teratoma can be found to contain very diverse tissue formation which, at least in part, may be identified as representing rudiments of organs, or perhaps even fully developed organs which, however, are superfluous for the individual in whom they are found, we may consider such a tumor as a heterochthonous teratoma, or as a bigerminal implantation, *i.e.*, as a rudimentary twin which is more or less completely enveloped by the well-developed twin. On the other hand, if the teratoma contains only diverse tissues and cysts whose production does not necessarily imply the existence of a second division, the tumor may be looked upon as autochthonous teratoma, or as a monogerminal implantation." Montgomery,[27] in a paper concerning a sacral teratoma which contained a scapula, has reiterated this principle.

In this regard it has been mentioned above that the mother of the infant in our case was a twin sister and had other twin sisters. The family history of twin pregnancies and the form of the external tumor of the infant might suggest that it was of heterochthonous origin, but both gross and microscopic study refute any such inference.

(*H*) Budde [28] has advanced the theory that the internal teratomas are genuine tumors which result from infoldings of the three primary germinal layers with the division of the blastopore. This theory could explain the origin of the various teratomas such as mediastinal, lumbosacral, sacral, cervical, and so on, which originate in the midline. They are most apt to arise when organs or organ systems are budding. The same author also considers that only the external malformations are rudiments of twins.

(*I*) Theories of origin from the fast growing structures of the caudal extremity of the early embryo. The intimate relation of the neurenteric canal, *i.e.* the channel connecting the alimentary canal and neural tube, the postanal gut and the coccygeal remnants of the neural tube are well described by Grosser, Lewis and McMurrich.[29] These structures are considered by many adherents to the monogerminal theory to be a fruitful source of sacrococcygeal teratomas. Middeldorpf [30] first attributed the origin of sacrococcygeal teratoma to the postanal gut. He described a cystic fatty tumor containing a structure resembling intestine. This was adherent to the rectum and had an external opening. Bland-Sutton[31] also thought that

retrorectal sacrococcygeal teratomas arose from the postanal gut. Hundling[32] concluded that "remains of the lower neural canal and the postanal gut appear to form the basis for many of the ventral tumors," and that all the body tissues may be represented.

Galletly included the neurenteric canal as a possible source of origin of congenital presacral tumors. Hansmann believed that the neurenteric canal or its remnants are a source of these tumors and found that they were in relation to the spinal canal, either intra- or extradural, and associated with anterior sacral defects. He recognized that tissue from the filum terminale could produce similar tumors. Hansmann and Berne implied that definite proof of origin in the neurenteric canal could be predicated upon the presence of an anterior sacral defect. Ewing supports the neurenteric canal theory in quoting the cases of Hildebrand, Jasterboff and Ritschl, and von Bergmann.

The tumor in our case did not contain organs or any well formed rudiments of organs and, therefore, it is assumed to be of monogerminal or autochthonous origin. It was large and well encapsulated, filling the pelvis, and extended out into the perineum. Anterior sacral defects were not present, nor was there any connection with the spinal cord, its terminations or coverings. Therefore, it is not likely to have originated from the neurenteric canal.

The tumor was attached deeply into the posterior wall of the rectum at a site which approximated the junction of the embryonic postanal gut with the primitive gut. The hypothesis that the tumor originated solely from the postanal gut is opposed by absence of intestinal mucosa in the tumor or its pedicle. Budde's concept of the infoldings of the primary germinal layers could be considered as explaining the complex histological picture. However, the attachment of the tumor to the rectum cannot be dismissed summarily. It is felt that in some way the postanal gut was involved in a snaring-off process with complexes of cells from other tissues. This probably occurred during the full embryological development of the postanal gut.

With the recession and disappearance of the postanal gut, which is a normal embryological process, the tumor attachment was carried into the rectal wall. In the meantime the complicated cell complexes continued to proliferate and ultimately formed the intricate teratoma found at autopsy.

## Summary and Conclusions

1. A case of a large, intra- and extrapelvic teratoma in a newborn infant is presented, the gross and histological findings being reviewed in detail.

2. Some of the literature concerning the incidence and theories of genesis is briefly reviewed.

3. There are criteria suggesting that the tumor in the presented case originated in relation to the embryonic postanal gut.

Note: The author wishes to express appreciation to Dr. Wm. F. Jacobs for his helpful criticism of the material in this paper.

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## DESCRIPTION OF PLATE

### PLATE 50

FIG. 1. Anterior view of fetus showing attachment of tumor.

FIG. 2. Lateral aspect of tumor mass. Note edema of lower extremities.

2

1

Rosedale Sacrococcygea Teratoma

# INTERVENTRICULAR SEPTAL DEFECT, DEXTROPOSITION OF AORTA, AND DILATATION OF PULMONARY ARTERY*

## REPORT OF A CASE WITH STRUCTURAL PATHOGENESIS

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Defects of the interventricular septum are not rare, their reported incidence varying from 225 cases in a statistical study of 850 cardiac anomalies,[1] to 5 in 753 cases.[2]

The combination of interventricular septal defect, dextroposition of the aorta and dilatation with hypertrophy of the pulmonary artery is "extremely rare," according to Baumgartner and Abbott.[3] Abbott has christened this association of defects the "Eisenmenger complex" because it was first described by Eisenmenger in 1897.[4] Search of the literature has revealed only one other similar case, which also has been published by Abbott.[5] It therefore is our purpose to report this as another case of what apparently is a very unusual condition.

## REPORT OF CASE

*Clinical History:* E. M., a white male, 10 years of age, admitted to the Buffalo City Hospital April 25, 1933, had been under observation in the hospital in both in and out-patient departments, for 4 years. His mother stated that there was transient "blueness" at birth. Since this time cyanosis and dyspnea have been manifested consistently with exercise or fright. He always has had a "shiny red complexion." Past illnesses were pertussis, measles, mumps and scarlet fever; the only operation was a tonsillectomy. There was jaundice for a week some years prior to admission.

Physical examinations made at intervals revealed the following: The right chest wall bulged somewhat anteriorly. The apical impulse, which was diffuse, was just medial to the right midclavicular line. Cardiac dullness extended 1 cm. beyond the left parasternal line. There was an apical systolic murmur and a snapping second sound in the mitral area. Moderate clubbing of the fingers was present. There was circumoral pallor, in contrast to cyanosis of the nail beds, ear lobes and mucous membranes of the mouth and lips. There were some carious teeth and gingivitis.

* This case was reported in abstract before the Buffalo Pathological Society, October 29, 1933.

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*Laboratory Studies:* The red blood cell count was 5,120,000 per cmm., hemoglobin 80 per cent (Sahli). Urinalysis was negative three times and once showed 2 plus albumin and many hyaline casts.

Electrocardiograms exhibited an inverted T wave in lead I, partial inversion of the Q. R. S., and left ventricular preponderance in leads II and III. Impression: congenital dextrocardia plus an enlarged left ventricle resulting from some congenital defect other than that of location.

X-ray, 1 year prior to last hospital admission, seven foot plate: Gt. Vs. 5.8; M. L. 7.7; M. R. 4.1; longitudinal 11.8; transverse 11.8 and thoracic diameter 21.2 cm. Diagnosis: dextrocardia. Previous X-ray studies since 1929 were the same, except for smaller dimensions.

The patient had been in his usual state of health until 2 days before admission to the hospital when he suddenly felt dizzy, weak and cold. Because of extreme cyanosis he was placed in bed the next day by his mother and the following day brought to the hospital.

In the hospital he complained of soreness of the throat and slight pain in the left ear. The throat was slightly reddened and the left ear negative. He had severe attacks of dyspnea and cyanosis, and the character of the cardiac murmurs changed. The liver became palpable 2 finger breadths below the costal margin. Death occurred the third day following a particularly severe interval of cyanosis and dyspnea. The temperature varied from 99.4° to 103.8° F., the pulse from 100 to 144 per minute, and the respirations from 26 to 38.

## Autopsy Report

The autopsy was performed 2½ hours after death. The body weighed 70 pounds and was 120 cm. in length. There was marked lividity of the ear lobes, lips and nails. The fingers were slightly clubbed. There were some anomalous lobes of both lungs. The spleen and liver and gastro-intestinal tract were passively congested.

*Anatomical Diagnoses:* (1) Interventricular septal defect, dextroposition of the aorta, hypertrophy and dilatation of the pulmonary artery, patent foramen ovale, *dextroversio cordis*, persistence of an enlarged but obliterated ductus arteriosus, anomalous great vessels. (2) Hypertrophy and dilatation of both ventricles. (3) Coronary thrombosis. (4) Passive congestion of the liver, spleen and gastro-intestinal tract.

## Description of Heart

The heart *in situ* was roughly quadrilateral in shape. In position it was so situated that its apex and slightly more than one-half of its presenting surface was to the right of the midline. Its long axis crossed the midline obliquely in a plane extending from the left midclavicular point to the middle of Poupart's ligament on the right. The base of the heart was approximately at right angles to the mid-

line. When viewed from the front the base had a pointed appearance because of the great hypertrophy of the infundibulum. The anterior surfaces of the right and left ventricles presented to an equal degree. Posteriorly the left ventricle, and some of the right, were in relation to the dome of the diaphragm.

The heart weighed 310 gm. The myocardium was firm and deep red in color. The walls of the right and left ventricles measured respectively 1.5 and 1.8 cm. in thickness. The musculature of the infundibulum was especially hypertrophied. The right ventricular cavity was approximately one-third larger than the left. The trabeculae carneae in both, especially the right, were greatly hypertrophied.

In what would correspond to the dorsal and superior part of the interventricular septum of the normal heart there was a defect measuring 3 by 2.5 cm. The borders of this were rounded. The anterior and interior parts of the septum were well formed, fleshy, and measured 1.2 cm. in thickness and 1.4 cm. anteroposteriorly. The anterior part of the septum was arched in the form of a ridge, posteriorly, superiorly and to the right, thus bounding these aspects of the interventricular foramen. This fleshy band just described was continuous with the posterior wall of the conus of the right ventricle (Fig. 3). The superior border was 1.4 cm. in thickness. Viewed thus from the right, the superior and posterior boundary of the interventricular foramen partly separated the cavity of the right ventricle from the aortic vestibule of the left; it also partly obstructed the dextroposed aortic outlet.

From the left side the interventricular foramen faced directly into the chamber of the right ventricle and upward into the aortic vestibule.

There was no membranous portion of the interventricular septum. There was the normal fibrous attachment, that is, the remnant of the embryonic aortopulmonary septum, between the first part of the pulmonary artery and the aorta. This was continued into the fleshy superior border of the interventricular foramen, where it ended abruptly (Fig. 3). The fibrous remnant of the aortopulmonary septum was continuous with the atrioventricular fibrous rings, as it normally is.

The tricuspid orifice was 8.7 cm. in circumference. There were three, well formed, normally disposed cusps. These were attached

to an enlarged papillary muscle in the floor of the right ventricle. The medial cusp was attached also by a muscular band 1.5 mm. thick to the inferior right margin of the interventricular foramen (Fig. 3), and by an elongated chorda tendinea which traversed the interventricular foramen to be attached to a small, medially situated papillary muscle on the posterior wall of the left ventricle. There was a slight amount of fibrous thickening of the posterior cusp of the tricuspid and the endocardium of the right auricle.

The right auricle was capacious. The right auricular appendage measured 6 by 6.6 cm. in its greatest diameters, and its musculi pectinati were enlarged.

The mitral valve ring measured 7.2 cm. in circumference. The cusps, chordae tendineae and papillary muscles were situated normally. The latter were moderately hypertrophied. The left auricular appendage measured 3 by 3.2 cm. in its greatest diameter; its musculi pectinati were about one-third as thick as those of the right auricular appendage.

There was a patent foramen ovale. This measured 0.5 by 1 cm. in its greatest diameter, and passed obliquely through the interatrial septum. Its borders on the right were raised and well rounded. Its left orifice was partly obstructed by two diametrically situated muscle bands (Fig. 2).

The pulmonary artery arose in normal position from the hypertrophied infundibulum of the right ventricle. The pulmonic orifice and artery respectively were 7 and 8.3 cm. in circumference, while the aortic orifice and ascending aorta, at a corresponding level, measured 4.3 and 4.2 cm. in circumference. The walls of the aorta and pulmonary artery were respectively 1.3 and 2.2 mm. in thickness.

The great arteries arising from the aortic arch were anomalous, falling somewhat into the fifth class of anomalous arteries described by Piersol. A non-patent ductus arteriosus measured 2 by 0.4 cm.

The coronary arteries were normally distributed. The posterior descending ramus of the left contained adherent thrombus.

## Discussion

In attempting to explain the genesis of the principal anomalies presented here, a good understanding of the embryology of the

human heart, particularly of the formation of the interventricular septum, is necessary. Practical knowledge of this sort is probably best acquired in studying the hearts of serially sectioned young human embryos. Such were used by the author recently in making Born wax-plate serial reconstruction models of the heart and endocardial cushions.[6]

The bulk of the interventricular septum is derived from the septum inferius. This appears as a myocardial ridge on the ventral caudal wall of the common ventricle about the fourth week of embryological development. It grows dorsally and cranially, the ventral and dorsal tips developing faster than the central portion, which consequently is concave toward the axis of extension. It possesses a single layer of endothelium which is continuous with that of the muscular trabeculae. The central, concave free edge of the primary interventricular septum is joined in part by the fused atrioventricular endocardial cushion mass, the proximal bulbar septum and the aortopulmonary septum. This central portion is recognized in the fully formed heart as the pars membranaceum, the undefended space, or Peacock's septum.

According to Tandler,[7] the anterior or ventral bulbar swelling, or the prolongation of the concave lower edge of the proximal bulbar septum, becomes continuous with the ventral prolongation of the septum inferius. The dorsal prolongation, the bulbar swelling B, grows to the right of the tubercle of the anterior endocardial cushion and is broadened and flattened. The interventricular foramen at this stage is bounded as follows. "If one follows the margin of the foramen interventriculaire, beginning with the posterior prolongation of the septum bulbi, it is found to be a spiral ridge that runs upward along the free concave border of the proximal septum bulbi, passing anteriorly into the edge of the septum interventriculaire, then along this downward and backward and finally upward again, to terminate at the right tubercle of the posterior endocardial cushion. . . . The opening so bounded unites not only the two ventricles, but also leads upward and to the right into the pulmonary artery and to the left and upward into the aorta."

Tandler explains the actual closure of the interventricular foramen through downgrowth of the proximal bulbar septum to reach the septum inferius, the right ends of the fused atrioventricular cushions contributing to a degree that cannot be estimated.

Laubry and Pezzi [8] in their lucid description add two factors to the simple mechanism of closure of the interventricular foramen described by Tandler, *viz.* thickening of the interventricular septum and a "budding" of the fused endocardial cushions.

Mall [9] states that the aortopulmonary septum blends with the cushions through a dorso-lateral wing, which is divided to encircle the right atrioventricular orifice (*cf.* Tandler). The more cranial limb unites with the right lateral endocardial cushion, and the caudal one unites with the right lower wing of the anterior endocardial cushion. This almost complete circling of the right atrioventricular orifice in the embryo is attested in the adult heart by the blending of the septum aortopulmonale (the tendon of the conus — see Gray's Anatomy) with the right atrioventricular fibrous ring at its attachment to the medial cusp. He found that the interventricular foramen in his embryo No. 353, 11 mm., "is bounded above by the union of the septum aortopulmonale and the anterior cushion, in front by the septum aortopulmonale, behind by the extended portion of the posterior cushion and below by the muscle of the interventricular septum." As the aortopulmonary septum and the septum inferius approach, the vestibule of the aorta is shifted more and more to the left, so that when the pars membranacea septi has formed, the aortic vestibule is transferred to the left ventricle, leaving the pulmonary infundibulum in the right ventricle.

Keith [10] felt that as the infundibulum of the bulbus cordis expanded, a band of muscle arising from the infundibular septum fell across the interventricular foramen and with the endocardial cushions occluded it. Careful study of serially sectioned young human embryos at our disposal failed to reveal any such bands.

Frazer [11] believes that the first requirement for separation of the ventricles is disappearance of the bulboventricular ridge and a portion of the adjacent bulbus and ventricular wall. It is his opinion that the interventricular foramen never disappears, but remains patent as the opening from the left ventricle into the aortic vestibule.

With the apposition of the atrioventricular endocardial cushions, the shifting of the septum inferius to the right, the prolongation of the right bulbar ridge and the ablation of the bulboventricular ridge, the axis of the aortic channel is directed toward the left ventricle, which is increasing in size. The fusing lower ends of the proximal bulbar swellings join with the free edge of the septum inferius, to

which there is accretion of the trabeculae. Through this process the bed of the aortic channel is composed of part of the dorsal atrioventricular endocardial cushion and the right tubercle of the ventral cushion. With further growth of the bulbar swellings, the cranial portion of the right atrioventricular orifice is closed and remains as a part of the floor of the aortic vestibule, only the caudal portion of the right atrioventricular orifice remains as a permanent opening. In this manner the septum membranaceum is formed, the aorta is directed into the left ventricle and the infundibulum of the bulb remains to conduct blood from the right ventricle into the pulmonary artery.

Frazer's theory, which seems the most logical, would leave one the impression that the right ventricle is the truest representative of the primary heart tube, while the left ventricle is simply a diverticulum of the former, the ostium of the diverticulum being directed from the right ventricle into the aortic vestibule.

Disparity in size of the pulmonary artery and aorta is frequently explained as the result of unequal division of the embryonic truncus and bulbus arteriosus. In this case, however, the equality of the remainder of the aorta with the ascending portion attests to an equal division of the truncus and bulbus. The cause, therefore, must be sought elsewhere.

One can only speculate as to which factor involved in the closure of the interventricular septum has been defective here. The presence of normally disposed atrioventricular fibrous rings, valves and the intact lower part of the interatrial septum should be predicated on the fulfilment of most of the growth functions of the endocardial cushion material. The fibrous union between the roots of the ascending aorta and pulmonary artery, which is here continued into the anterosuperior crescentic margin of the muscular interventricular septum, would also suggest that the aortopulmonary septum had developed but failed to reach the interventricular foramen. However, such failure alone would not likely give rise to such a large opening. If one follows Frazer's theory, the large interventricular foramen could be explained as failure of the lower part of the bulbar ridges to fuse. If such occurred, dextroposition of the aorta would result from failure of the aortic vestibule to be shifted to the left.

The partial obstruction of the aortic vestibule by the posterosuperior border of the interventricular foramen would tend to cause

blood to be shunted from the left ventricle into the right, from whence its reflux would be partly prevented by the relation of the medial tricuspid cusp to the interventricular foramen. The disposal of an increased quantity of blood by the right ventricle would lead to its dilatation and hypertrophy, and also dilatation and hypertrophy of the pulmonary artery. In this respect the condition is much like that described by Abbott,[3] who has written " . . . for the pulmonary conus in the case here described is roomy and thick-walled, and leads into a very large and greatly dilated pulmonary artery (8.5 cm. wide). Both conus and artery have here developed as in the normal heart, and have evidently undergone dilatation to accommodate the additional volume of blood received from the left ventricle through the defect in the left to right shunt that prevailed owing to the relatively higher pressure in the left ventricle, while the dextroposed aorta received a mixed current of venous and arterial blood from both ventricles above which it rides and transmits to the systemic circulation, producing a raised oxygen — unsaturation in the capillaries there with resultant cyanosis." The dextroposed aorta was in a position to receive some blood from the right ventricle. The amount of venous blood in the systemic circulation would tend to be increased with increase of pressure within the right ventricle. This would account for cyanosis during exercise.

## Summary and Conclusions

1. The rare combination of interventricular septal defect and hypertrophy and dilatation of the pulmonary artery is presented and described.

2. The theories concerning the formation of the interventricular septum are reviewed. Of these, that advanced by Frazer [11] affords a reasonable explanation of the defects in this case.

Note: The author wishes to express appreciation to Dr. Wm. F. Jacobs, Pathologist, Buffalo City Hospital, for helpful criticism, and to Dr. W. J. Atwell, Professor of Anatomy, University of Buffalo Medical School, for his kind assistance and loan of serially sectioned human embryos from his collection.

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## DESCRIPTION OF PLATES

### PLATE 51

FIG. 1. Anterior aspect of heart and lungs. Note the partial turning of the heart to the right, its rhomboidal shape and the prominent pulmonary infundibulum. The anomalous lung lobes are also apparent.

FIG. 2. The interventricular septal defect, as seen through the opened left ventricle. Note that the chordae tendineae of the medial cusp of the tricuspid valve are attached in the floor of the defect. The hypertrophy of the left ventricle wall is evident.

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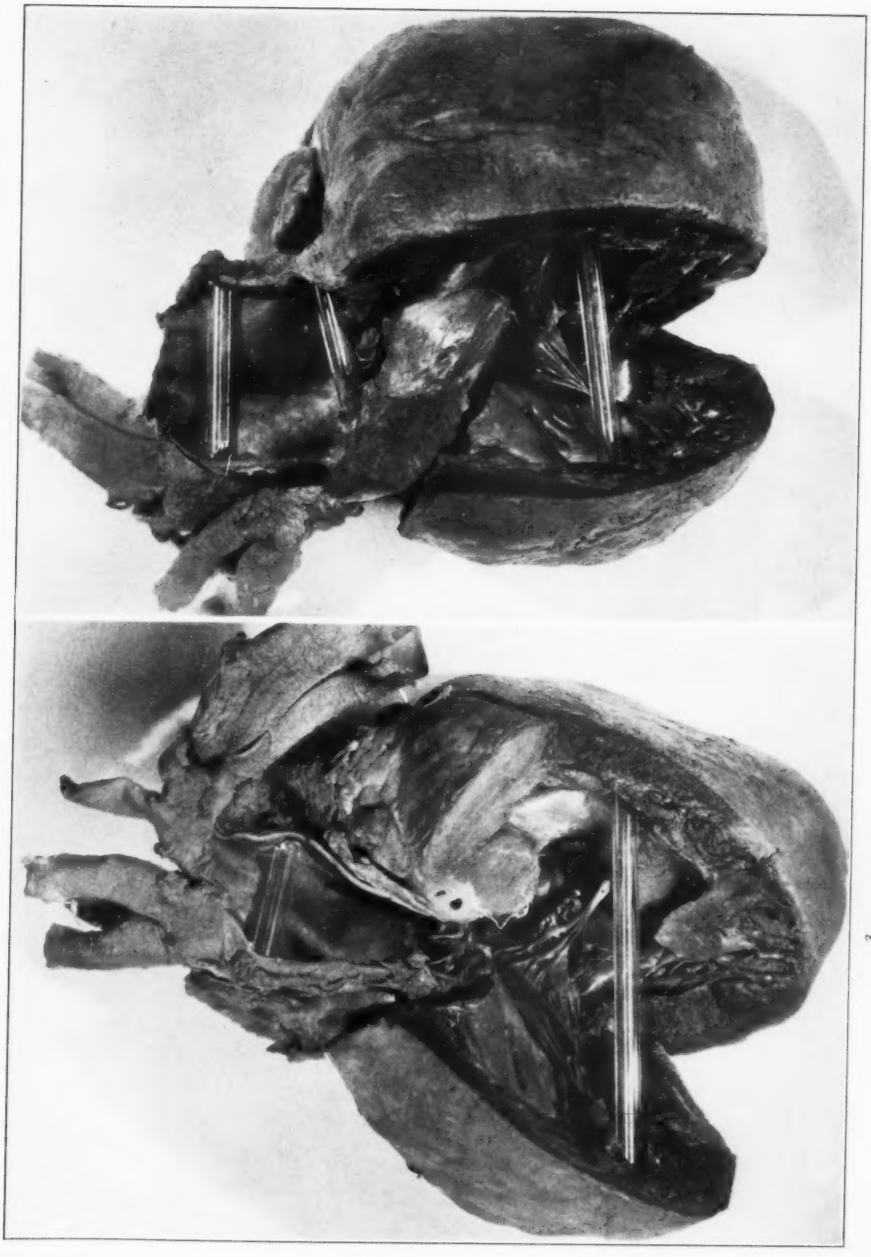
Rosedale Interventricular Septal Defect

PLATE 52

FIG. 3. Interventricular septal defect viewed through the opened right ventricle. The hypertrophy of the musculature of the right ventricle and pulmonary infundibulum is seen. Note the dextroposed aorta and the obstructing, thick posterior wall of the pulmonary infundibulum. There is coarctation of the arch of the aorta. Compare the size of the ascending aorta with that of the corresponding portion of the pulmonary artery in Fig. 4.

FIG. 4. The right ventricle is opened and the walls of the pulmonary infundibulum spread apart. Compare the diameter and thickness of the pulmonary artery with that of the aorta in Fig. 3.



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Rosedale

Interventricular Septal Defect

# A MALIGNANT HEMANGIOMA OF THE LUNG WITH MULTIPLE METASTASES *

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Malignant hemangiomas with metastases by way of the blood stream are extremely rare. Wright,[1] in 1928, described such a case and stated that less than a dozen reports of proved cases of this group could be found in the literature. The same statement is true today. He reviewed briefly the reports of the following authors: Borrmann,[2] Ewing,[3] Shennan,[4] Homans,[5] Langhans,[6] Theile,[7] and Jores.[8] Attention was called to the fact, however, that of these seven reports only the last three qualified as regards malignancy of the primary tumor. Wright's case should be classed with those of Langhans, Theile and Jores. Dassel's [9] case should also be included in the latter group.

Schlopsnies,[10] in 1930, gave a fairly complete summary of the reported cases of multiple angiomatous tumors. The summary includes multiple benign angiomas, angiosarcomas, multiple "system" tumors and *malignant metastasizing hemangiomas*. He classified his own case as an angiosarcoma of the spleen with multiple foci confined apparently to the hemopoietic system. In addition to this case, the reports of Grabowski,[11] Shennan,[4] and Wollstein[12] should be included among the hemangiomas with multiple foci but histologically benign. It is somewhat doubtful whether or not the angiosarcomas should be included in the group of malignant hemangiomas, since many of these may be only vascular sarcomas and not true tumors of the vascular system.

## REPORT OF CASE

*Clinical History:* L. P., a married, white female, aged 40 years, was seen by a physician on Nov. 28, 1933, at which time she complained of severe pain, of 6 weeks duration, in the right hip; backache, the onset of which was concurrent with the last menstrual period 6 weeks previously; weakness, insomnia, mental

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depression and nausea of 1 weeks duration, with some vomiting. She had had influenza in 1918, "heart trouble" and rheumatic fever at 16 years of age.

Her father had hypertension, and her mother had a manic depressive psychosis. Her brothers and her husband are living and well. During the past 18 months the husband had lost his business and at the time of the patient's illness necessities were being provided by other members of the family. Three pregnancies had resulted in three normal deliveries. The children, aged 16, 9 and 6 years, are normal.

*Physical Examination:* This revealed a pale, but well developed, well nourished woman of about 40 years. The positive findings were mitral stenosis and regurgitation, pulse 136, blood pressure 105/88. There was a tiny cervical polyp protruding slightly from the cervical canal.

Examination of the blood showed a hemoglobin of 40 per cent, red blood cells 3,100,000, white blood cells 5600, with the following differential count: polymorphonuclears 60, lymphocytes 31, monocytes 4, eosinophils 2, and basophils 2.

The patient was exhausted by the examination and wept most of the time. Her physician advised rest in bed, preferably in a rest home or sanitarium with supportive treatment. Bromides were prescribed as a sedative.

*Course of Illness:* On Dec. 2, 1933, the patient was cheerful, was eating well and nausea had disappeared. The pain in her hip was relieved. The blood pressure was 120/84, the pulse 90. Improvement continued until December 17th. At that time the hemoglobin had risen to 48 per cent and the red blood cells were 3,900,000. The pulse had dropped to 88.

From Dec. 17, 1933 to Jan. 7, 1934, there was recurrent pain in the right hip, for which it was necessary to use codein, as salicylates failed to relieve the pain. On January 7th, at 2 A.M., the patient complained of a severe sharp pain in the right chest. She was sent to a private hospital where she remained for a week. Examination revealed a small area of consolidation at the base of the right lung. There were râles over this area and increased density of the mediastinum. The patient was dyspneic. The temperature was 100.4° F., the white blood count 5800. It was believed by the physician in charge that the patient had developed pneumonia, possibly tuberculous in origin. While in the hospital the patient's temperature fluctuated from 101.8° F. to normal.

On January 13th the patient returned home. Her condition continued steadily downward. Three days before death, the physician was permitted to call a cardiologist and a surgeon in consultation. A diagnosis of acute cardiac decompensation, internal hemorrhage and shock was made. The patient's physician had previously made a tentative diagnosis of a malignant pelvic tumor with pulmonary metastases.

The patient was admitted to the Los Angeles County Hospital where examination revealed a pale, slightly yellowish, dyspneic and extremely weak, white female. There was flatness over the chest from the right base to the second rib. Breath sounds were distant or absent. The left lung field was resonant. The heart was displaced to the right, the rate rapid but regular. Blood pressure at this time was 80/40. Examination of the abdomen showed that the liver was displaced downward about 1 inch below the costal border. No masses and no tenderness were found.

It was thought that hemorrhage had taken place into the right pleural cavity, probably from pulmonary metastases. A thoracentesis yielded 200 cc. of bloody fluid, and 150 cc. of air was replaced.

A blood examination showed 30 per cent hemoglobin, 2,380,000 red blood cells and 14,700 white blood cells. The urine was essentially normal.

While preparations were being made for a transfusion the patient died suddenly.

## Autopsy Report

The autopsy was performed 3½ hours postmortem. The body is that of a well developed, well nourished white female about 40 years of age. The skin and mucous membranes are pale. The superficial lymph nodes are not palpable and there is no edema. The diaphragm level is at the fifth rib on the right, the sixth rib on the left.

On removing the sternum about 3000 cc. of bloody fluid is found in the right pleural cavity and about a liter of somewhat bloody fluid is found in the left pleural cavity.

The pericardium is normal. The heart weighs 240 gm. and is normal, except for the right coronary which has no opening into the aorta, although the artery, which is smaller than normal, is found in the epicardial fat about 1 cm. from the aorta. There is a small dimple in the aorta opposite the right aortic cusp at the usual site of the coronary orifice.

The right lung is almost completely collapsed; the left lung is partially collapsed. The right lung weighs 330 gm. and forms a mass a little larger than a man's fist (Fig. 1). All three lobes are quite firm, except a small portion of the upper lobe which contains air. In the pleura of the interlobar and posterior surfaces of the upper lobe, and throughout the middle and lower lobes, are a number of raised, reddish black tumor nodules which appear to contain blood. These vary from 0.2 to about 1 cm. in diameter. In places, several of these nodules are more or less confluent. At the lower border of the lower lobe there are several larger, granular red areas covered more or less with a buffy coat of fibrin. The largest of these measures 5 by 1.5 cm. These are angiomatous tumor masses with some hemorrhage into the pulmonary tissue surrounding them. There are approximately 50 hemorrhagic nodules scattered throughout the pleura. On the cut surface an occasional similar nodule is seen deep in the lung tissue, but the greater number are pleural and subpleural.

The left lung is slightly larger than the right, but weighs only 290 gm. About one-third of the upper lobe and a small portion of

the upper part of the lower lobe are air-containing. Hemorrhagic nodules similar to those described are found throughout the surface of the lung but they are not so numerous as in the right lung. In the diaphragmatic surface of the lower lobe there is a larger tumor measuring 2 by 1.5 by 1.5 cm. Occasional hemorrhagic areas are found on the cut surface. Some 20 to 25 pea-sized, hemorrhagic tumors are found scattered over the parietal pleura of the right side and 12 to 15 similar ones on the left. These are localized over the intercostal muscles.

The spleen weighs 120 gm. The capsule is smooth, the pulp pale red with distinct markings. Two small accessory spleens are found near the hilum which measure 0.6 and 1.2 cm. respectively.

The adrenal glands and kidneys are normal.

The uterus is slighly enlarged. The tip of the cervix is rather large with a smooth surface. There is a tiny polyp projecting from the cervical canal. The uterine cavity is normal. The ovaries are slightly cystic. The tubes are normal.

The duodenum, bile ducts, stomach and pancreas are normal except for marked pallor.

The liver weighs 1800 gm. In the anterior portion of the liver a number of grayish red, poorly defined, metastatic nodules may be seen through the capsule. On the under surface, just to the right of the gall-bladder, there is an elevated nodule 2 cm. in diameter, which is dull red with a few pale grayish areas showing through the red background. On the cut surface the nodules vary from 0.3 to 1 cm. in diameter, and show the same mottled reddish gray color. The remaining portion of the liver is pale and the markings are rather indistinct. The gall-bladder and contents are normal.

There are a number of small, hemorrhagic tumors in the fat surrounding the pancreas. None is found, however, within the body of the gland itself. Immediately below the head of the pancreas there is a firm, rounded mass measuring 8 cm. in diameter and consisting of a group of 12 to 15 enlarged hemorrhagic lymph nodes surrounded by fibrous fatty tissue. The largest of these nodes measures nearly 2 cm. in diameter. Most of them are reddish black, due to the large amount of blood present. Several, however, show small grayish spots scattered through them, while the more cellular ones contain considerable grayish tissue. Similar enlarged nodes are found on either side of the aorta almost to the

bifurcation. The aorta is somewhat smaller than normal. Occasional yellowish streaks are seen in the intima.

The bone marrow of the sternum is pale red and of normal consistence.

The dura and leptomeninges are normal. The convolutions over the convexity of the brain appear slightly flattened. The brain tissue is exceedingly pale. The large vessels at the base of the brain are distinctly hypoplastic and show an occasional atheromatous spot.

A rapid frozen section through one of the nodules from the lung and also one from the liver revealed cellular angiomatous growths showing malignant characteristics.

*Anatomical Diagnoses:* Malignant hemangioma of right lung; malignant hemangioma, metastatic, left lung, parietal pleura, liver and retroperitoneal lymph nodes; fatal hemorrhage into right pleural cavity; anemia, secondary; congenital malformation of heart (imperforate right coronary); hypoplasia of aorta and cerebral vessels, and multiple accessory spleens.

## Histological Examination

*Retroperitoneal Lymph Node:* The body of the gland is surrounded by a dense fibrous capsule. The lymphoid tissue is completely replaced by a vascular tumor consisting of a cavernous part and a more cellular part. In the cavernous part are many large spaces filled with red blood cells. These spaces are lined for the most part by the usual flattened endothelial cells. The partition walls are rather thin in most places, but occasionally spread out into fairly broad fibrous bands. An increased proportion of polymorphonuclear leukocytes is seen in the spaces among the red blood cells.

In the cellular part the blood spaces are small and partially or wholly collapsed. Only a few of the open ones contain red blood cells. The cells lining these spaces are very atypical. Some are more or less elongated, hypertrophied endothelial cells, while others are large polygonal cells with oval or spherical nuclei, many of which are hyperchromatic (Fig. 3). All gradations between these two extremes may be seen. Surrounding the spaces, or in the more cellular areas, the same kind of cell is predominant. Mitoses can be found in nearly every high power field. In many places the

stroma is loose and edematous with abundant fibrin present and considerable numbers of polymorphonuclear leukocytes.

In some of the lymph nodes the tumor tissue is arranged in whorls and papillary extensions (Fig. 2). The lymphoid tissue is almost wholly replaced by a turbulent-appearing tissue. There are numerous smaller and larger blood spaces, some of the latter forming long sinuous channels among islands and promontories of cellular tissue.

Many nucleated red cells, mostly normoblasts, are found in the vascular spaces. In one small space practically filled with normoblasts seven cells were counted. Many of these cells show the nuclear material broken up and scattered through the cell as dark staining fragments. Occasional megaloblasts are seen also. In addition to the above, many polymorphonuclear neutrophilic leukocytes are present, also moderate numbers of lymphocytes, a few eosinophils and occasional basophils.

*Lung (Right):* Sections through one of the vascular tumors at the base of the right lung show a number of large cavernous spaces in the pleura. Cellular, moderately malignant areas, similar to those described, border the larger spaces. The partition walls of the large sinuses are broken down in some instances and the blood is clotted. Over the surface is a layer of fibrin of irregular thickness. It was evidently from these large, coalesced blood sinuses that hemorrhage occurred into the pleural cavity.

Moving inward from the periphery one sees a peculiar arrangement. The blood spaces are relatively small, many of them collapsed. The open ones contain red blood cells and groups of extremely large phagocytic "dust cells," the latter containing either red cells in various stages of disintegration, or coarse clumps of brown pigment (hemosiderin). The septa are thick and quite vascular. Large, swollen polygonal cells line the spaces. The nuclei are large, oval or spherical, and some are hyperchromatic. These areas, no doubt, represent collapsed lung in which small hemorrhages have occurred because of the presence of metastatic tumor. In addition, there is active phagocytosis of red blood cells and all the alveolar lining cells appear to be hypertrophied.

The bronchi are nearly all large and irregular. The lining epithelial cells show hypertrophy and crowding. Many of the nuclei are pyknotic.

*Liver:* The nodules in the liver are roughly spherical and fairly well circumscribed growths having the characteristics of metastatic rather than primary tumors. These consist in part of angiomatous and cavernous spaces filled with blood and partly of very cellular areas similar to those described above. The angiomatous portion gradually merges into the cellular, more malignant areas. In some of the latter there is a tendency to form a papillary type of growth. In one place a medium sized vein (3 mm. greatest diameter) shows tumor growing completely through the wall at one side. Tumor is heaped up on the inside of the vessel and spreads along the wall for some distance on both sides. At one end of the same vessel a similar phenomenon has occurred. The liver cells are swollen, the cytoplasm is finely granular and pale staining. The Kupffer cells are normal.

*Spleen:* The capsule is of uniform thickness and the trabeculae are moderately thick in places. The reticulum is everywhere thickened and appears to be somewhat edematous. Large, early fibroblastic cells are also present. The littoral cells of the venous sinuses are large, with round or plump oval nuclei. Occasional, large, atypical tumor cells are found free in the sinuses. The lymphoid follicles are rather small. The malpighian arteries are moderately thickened and show some hyaline degeneration.

*Kidney:* Essentially normal.

*Pancreas:* Normal.

*Bone Marrow (Sternum):* Stained with Giemsa, many myelocytes, a moderate number of eosinophilic myelocytes and many normoblasts are seen. The red cells show moderate anisocytosis and poikilocytosis and tend to be small. Occasional megakaryocytes are seen, and now and then a large irregular cell with oval nucleus, which is probably an atypical endothelial cell from one of the malignant areas.

## Comment

Wollstein,[12] in 1931, reported a malignant hemangioma of the lung in a female infant 4 months and 20 days old. She considers this the first case reported in which the principal tumor was found in the lung. Although the lung was the organ chiefly involved, it is not certain that this was the primary site. Shennan [4] presented an unusual case, a female, 23 years of age, who had a large angiomatous

tumor nodule near the root of the left lung. A larger mass involved the superior mediastinum. Because of the greater size of the mediastinal tumor and the peculiar barking cough suggesting mediastinal pressure, the author favored the mediastinum rather than the lung as the primary site. The spleen was enlarged by the tumor growth, and other tumors were found in the thymus, pleurae, mediastinal lymph nodes, liver and bone marrow. In Shennan's case the tumors were largely confined to the hemopoietic system, as in most of the "multiple foci" tumors. The tumors were histologically benign, further evidence in favor of a system disease neoplasm. The patient died of hemorrhage into one of the pleural cavities.

In the author's case a similar situation is seen in regard to the primary tumor as in the 2 cases referred to above. The marked dyspnea, the fatal hemorrhage and the more extensive growth of the tumor in the right lung point to this organ as the seat of the disease. On the other hand, the metastases in the lungs, pleurae and liver are more readily explained by assuming the primary growth to have been located in the retroperitoneal lymph nodes. The tumor-like mass found in the latter situation, together with the history of pain in the right hip for a period of 6 weeks, are further points in favor of this location. It is evident that no definite conclusion can be reached in regard to the primary site.

Regardless of our inability to designate the original growth with any degree of certainty, it is quite evident that the greater number of angiomatous nodules found in the lungs, pleurae, liver and lymph nodes are true metastases. Let us consider the nodules in the liver in this respect. The tumor masses all tend to be spherical and the surrounding liver tissue is normal except for occasional small hemorrhages. The Kupffer cells particularly show no abnormal changes. In the liver metastases both cavernous and cellular angiomatous structures are found. The malignant character is evident, not only by the anaplasia of the tumor cells, but also by invasion of the wall of one of the veins.

From the foregoing, there would seem to be no escape from the conclusion that the multiple tumor foci in this case are true metastases. The characteristics that distinguish a system disease tumor are largely lacking. Although the liver and the retroperitoneal lymph nodes are involved, the spleen is not involved and, so far as we know, the bone marrow likewise is free. Furthermore, the

distinctly malignant appearance of the tumor growth wherever encountered is contrary to the usual benign histological character of the system disease tumors.

The presence of congenital anomalies of the circulatory system in this patient may have etiological significance. Cohnheim's theory of tumor growth in aberrant or misplaced portions of organs or systems, which is well established for certain kinds of tumor, suggests itself as a probable causative factor. A definite congenital anomaly was present in the right coronary artery which failed to arise from the aorta in the usual way. A small dimple was present at the usual site opposite the right leaflet of the aortic valve. Lack of any evidence of syphilitic changes and the presence of only very early atheromatous lesions in the aorta make it quite certain that the condition is congenital. The aorta was moderately hypoplastic and the large cerebral vessels at the base of the brain were distinctly smaller than normal. Two small accessory spleens were found at the hilum of the main organ.

## Summary

1. A case of malignant metastasizing hemangioma, of which there are less than a dozen true cases in the whole medical literature, is reported.

2. The largest tumor was found in the right lung and death was due to hemorrhage into the right pleural cavity.

3. True metastases consisting of both cavernous and malignant cellular areas were found in the lungs, pleurae, retroperitoneal lymph nodes and liver.

4. The type cell is the endothelial cell which forms blood-vascular spaces in all the tumor nodules. The cells vary from practically normal appearing cells lining the cavernous spaces to extremely large atypical cells that almost fill the blood spaces in the more cellular areas. In the latter the growth is rapid and apparently highly malignant.

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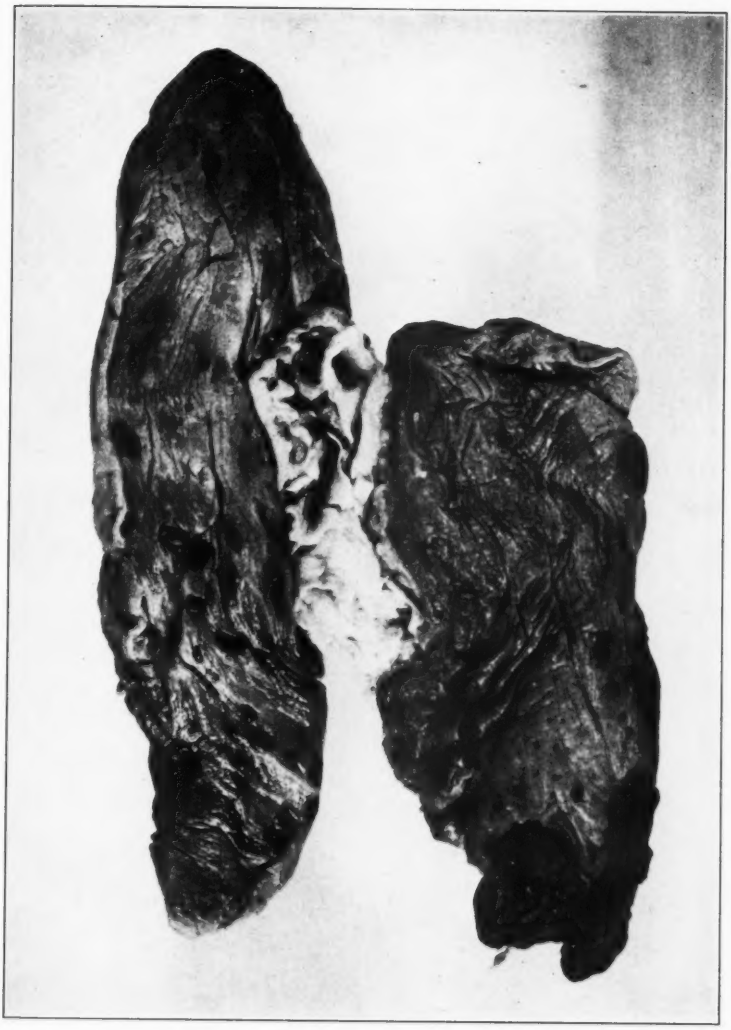
## DESCRIPTION OF PLATES

### PLATE 53

FIG. 1. The collapsed right lung (two-thirds normal size) showing the main tumor mass at the base of the lower lobe with hemorrhage into the surrounding tissue. A number of hemangiomatous nodules are seen in the pleura of the upper lobe, also along the lateral border of the lower lobe.



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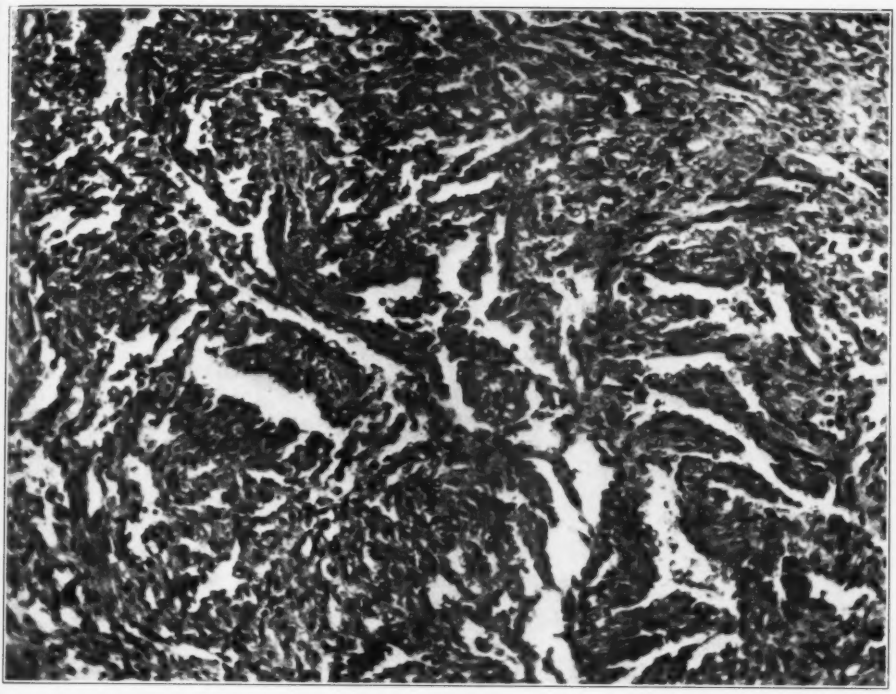
## PLATE 54

FIG. 2. Photomicrograph from section of retroperitoneal lymph node showing turbulent papillary type of growth completely replacing the lymphoid tissue. × 160.

FIG. 3. Photomicrograph from section of retroperitoneal lymph node showing marked anaplasia of the endothelial cells. Several mitotic figures are present in this field, but not all are in true focus. × 700.



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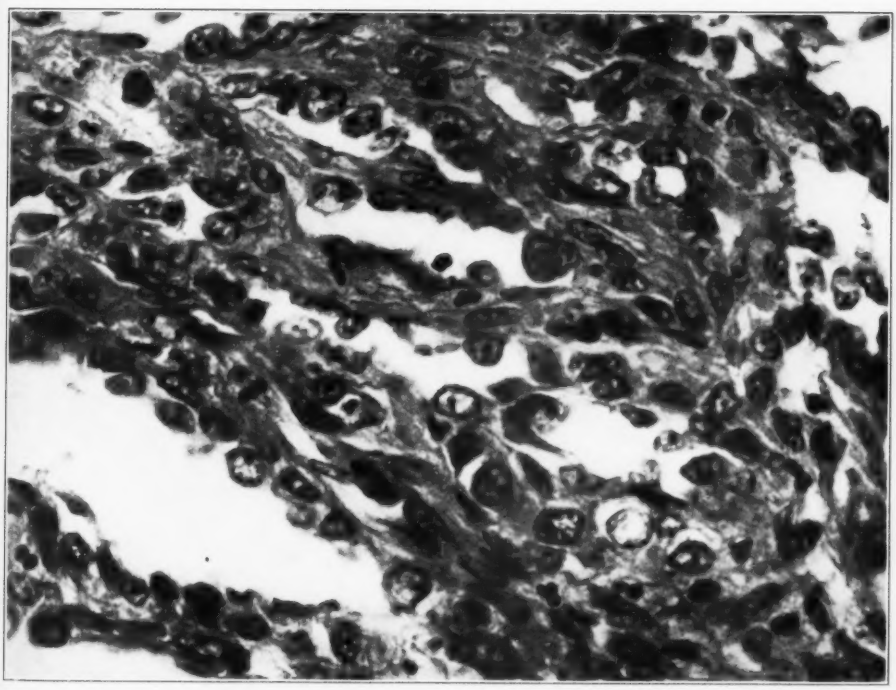

3

Hall Malignant Hemangioma of Lung

# ANTIGROWTH EFFECT OF LIPOID FRACTIONS OF TISSUE EXTRACTS *

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Under the relatively simple conditions that prevail in the cultivation of cells *in vitro* it has been fully established that certain constituents of the tissues and fluids of the body stimulate growth and that others inhibit it. Carrel [1] noted that the growth of connective tissue was more abundant in the plasma of young chickens than in that of older ones and, in 1921, Carrel and Ebeling [2] determined that the influence of age, as reflected in the serum of the animal, was exerted not by variations of growth-accelerating factors, but by fluctuating inhibiting agents. Later, in 1923, the same authors [3] separated the serum into a growth-activating and a growth-inhibiting fraction by precipitating the former by bubbling carbon dioxide through the diluted serum. Actually to accomplish indefinite multiplication of fibroblasts in artificial mediums it is required that the inhibiting effect of the plasma be counterbalanced by the addition of positive stimuli, especially in the form of embryonic juice or primary protein derivatives.[4, 5, 6] Very potent growth stimuli are present in the tissue of Rous chicken sarcoma. Sittenfield and Johnson [7] showed that the tumor-producing substance could be neutralized by mixing an active filtrate with blood, and subsequently recovered by buffering the mixture to a pH 4.0 and then extracting the resultant precipitate at a pH of 8.0 to obtain the active tumor agent in solution. This substance that neutralized the tumor principle was later found by Sittenfield, Johnson and Jobling[8] to be confined to the globulin fraction of serum. Information concerning the growth regulatory mechanism which operates in the living animal has been slower to appear. So far as is now known types of growth such as embryonal, regenerative, compensatory and even neoplastic, may take place in response to stimulating and re-

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tarding influences analogous to those of the artificial culture. Most of the investigative successes have been concerned with inhibiting agents. Certain of the hormones, when administered in excess of the normal requirements, inhibit multiplication of the cells that produce them. Loeb [9] found that thyroid feeding of partially thyroidectomized animals inhibited regeneration of the thyroid remnant. It has been shown by Cameron and Carmichael [10] that thyroxin diminishes not only the growth rate of the thyroid gland but of the body as a whole. In our experiments with parathyroid hormone [11] and insulin [12] the hormones in excess of normal requirements were supplied to the animal. Such excesses cause departures from the normal metabolism of the animals and the decreased karyokinetic rates observed by us may have been secondary to disturbed cell nutrition.

It was considered desirable to examine tissues not known to produce internal secretions for the presence of inhibiting agents. The kidney was chosen because of its known quick regenerative response after unilateral nephrectomy and its great growth activity in rats during the first month of life. It was readily demonstrated that the kidney contained inhibitory substances which could be extracted by dilute acids and by acid alcohol.[13] A quantity of the acid alcohol extract equivalent to about 2 gm. of the fresh kidney was found to inhibit tubule cell proliferation. In experiments described below, evidence is presented to show that the chief inhibiting agent is of a lipoid nature, that its distribution is probably wide, since it was demonstrated in several tissues, and that it inhibits mitotic proliferation, not only of the kidney but also of the liver.

## Method of Bio-Assay

The technic of determining the proliferative activity of the renal epithelium is now essentially the same as that described in the earlier report.[13] With the number of litters tested well above 100, it has been found that the mother rats should be kept upon an adequate commercial mash reinforced by alternate daily feedings of cheese, fresh meat or fresh cabbage and during the winter months with dry brewer's yeast. Litters 18 to 21 days of age are best and at least two litter-mates from each litter should be reserved for controls. The young rats were injected intraperitoneally and killed 24 hours

later. From the formalin-fixed right kidney there was cut a 3 mm. transverse block midway between the two poles. From the center of this block, embedded in paraffin, 8 micron ribbons were cut for staining in hematoxylin and eosin. The mitoses of the tubular epithelium were counted in two or three sections and, if the variations were considerable, several additional sections were examined.

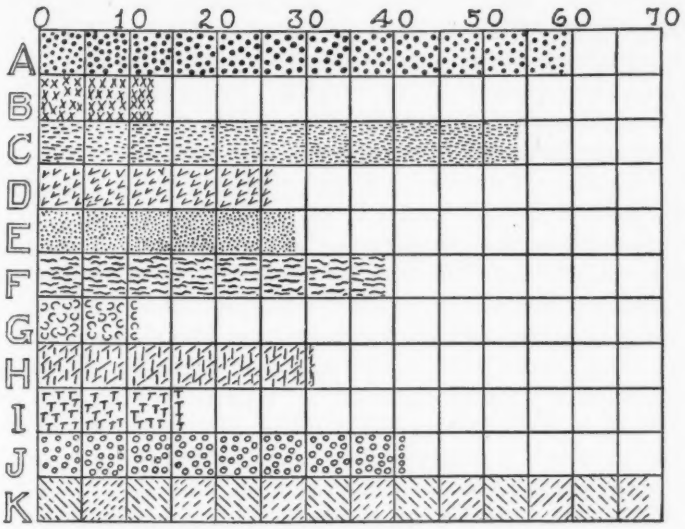


CHART 1

A–K inclusive represent doses of lipoid-containing extracts which are described in the text. All doses were converted to the equivalent amount of fresh tissue represented by the extracted material. The percentages from 0 to 70 represent the reduction of the mitotic rate per gram of fresh tissue and are based on results of two or more littermates injected with the extract.

Although the procedure gave much uniformity, little or no weight was given to minor decreases in the mitotic rate.

## LIPOID NATURE OF THE INHIBITING AGENT OF TISSUE EXTRACTS

In several preliminary experiments there were obtained indications of acute inhibitory effects following the administration of fresh tissues. Fresh macerated rat kidney was thoroughly mixed with 2 volumes of physiological saline solution and after standing 5 minutes the coarse particles were removed by straining through

muslin and centrifuging at low speed. The cloudy supernatant liquid rich in suspended cells gave marked inhibition ("A," Chart 1). After removal of suspended material by filtration the clear filtrate had little effect on the mitoses. When dilute alkali was substituted for the physiological saline solution much less inhibition was seen ("B," Chart 1). No attempt was made to explain the low inhibitory effect of the alkaline extracts, but in subsequent extractions alkali was avoided. The part played by the suspended cells is discussed later in connection with the residue. The efficiency of acid alcohol extraction is illustrated in "C," Chart 1. Unlike the two preceding extracts which were cloudy suspensions, Extract "C" was rendered perfectly clear by the following procedures: fresh kidney pulp was mixed with 3 volumes of 0.2 per cent solution of HCl in 60 per cent alcohol and allowed to stand for 18 hours. Sufficient alcohol was then added to raise the alcoholic concentration to 86.6 per cent. Separation of the clear extract was obtained by filtration. The routine procedure in preparation of this and subsequent extracts was to evaporate the solvent by fanning, to suspend the residue in distilled water and to adjust the reaction to pH 7.4. Residues of the various solvents employed (acetone, chloroform, ether, alcohol) were tested to determine the inhibiting effects of their residues. Likewise NaCl in excess of that present in any of the extracts was injected and found to be non-inhibitory. In Extract "C" not only was the potency of the extract found to be high but the inhibiting substance was shown to be soluble in 86.6 per cent alcohol. Simple alcoholic extractions were then made and the amount of inhibitor appearing in the extracts was found to increase with the concentration of the alcohol ("D" with an alcoholic concentration of 63.3 per cent, "E" with 86 per cent, and "F" with 95 per cent, Chart 1).

With the data indicating that the inhibiting substance was of a lipoid nature, more effective lipoid extractions were inaugurated in attempts to increase the yield of inhibitor. A single 7 hour extraction of kidney desiccate with chloroform gave only 11 per cent inhibition ("G," Chart 1), but a 6 hour extraction with warm chloroform in a Soxhlet extractor yielded a product with a potency of 31 per cent ("H," Chart 1). Following an initial extraction of kidney with acetone, Soxhlet extraction with anhydrous ether for 22 hours gave 17 per cent inhibition ("I," Chart 1). Acid alcohol extracts were almost completely dissolved by chloroform. In one in-

stance 2.03 gm. was removed from 2.18 gm. acid alcohol extract by 7 hours Soxhlet extraction with anhydrous chloroform.

Many extractions have been made for the purpose of increasing the yield of inhibitor per gram of fresh kidney. Maclean [14] pointed out the relative inefficiency of ether or chloroform alone for the removal of lipoid and called attention to the better yields obtained by ether (or chloroform) extraction followed by alcohol. After dehydration of fresh kidney pulp with 10 volumes of acetone, a combined extraction with chloroform and alcohol gave a product causing a 40 per cent inhibition ("J," Chart 1). Maclean and Maclean [15] now recommend 4 to 6 extractions with cold absolute alcohol. By this method we obtained no greater degree of inhibition (36 per cent). Jowett and Lawson [16] have recently described a method for the quantitative extraction of lipoids by subjecting the powdered material to three 1 hour extractions with the hot absolute alcohol. We first dehydrated by covering the macerated tissue with absolute alcohol and then gave the material 6 consecutive 1 hour extractions with hot absolute alcohol. The seven fractions were combined and tested. The average inhibition was increased to 68 per cent ("K," Chart 1), which is the best result so far obtained. This is the mean of an 18 day and a 20 day litter of rats. The details of the 20 day litter are given in Table I. It is seen that effective inhibition was accomplished by as small an amount of lipoid as that contained in 0.5 gm. of fresh kidney.

### Type of Lipoid Responsible for the Inhibitory Effect

Although no systematic attempt has been made to fractionate the constituents of the lipoid extract, several of the experiments point to the lecithins as the active agent. First the strength of the inhibitor was found to increase in proportion to the efficiency of the lipoid extraction. The extracted desiccated material dissolved readily in either anhydrous ether or anhydrous chloroform. When acetone was used as a dehydrating agent it removed some of the inhibitor and it contained not only cholesterol and neutral fat but also phospholipids. In one instance the phosphorus content of the acetone fraction was 1.73 per cent. Determinations of N and P in the usual ether-alcohol extract of kidney by the Maclean [15] method showed an N of 3.12 per cent and a P of 2.79 per cent. Pure cho-

lesterol (Kohlbaum) in a dose of 120 mg. was devoid of inhibiting property while lecithin (practical, Eastman) in a dose of 117 mg. produced 56 per cent inhibition, which compared favorably with the inhibition produced by the lipoid kidney extract. A pure lecithin * which had stood in a desiccator for more than 12 years was toxic and lethal to the rat in a dose of 180 mg. and a 11 mg. dose gave a 70 per cent inhibition. Hydrolysis had certainly taken place in

TABLE I

*Experiment 49*

*Injection of Kidney Lipoid Extract (Jowett and Lawson Procedure)*

| No. of rat | Age | Weight at injection | Dosage | Dosage equivalent of fresh kidney | Weight at autopsy | Average No. mitoses per section of kidney |
|---|---|---|---|---|---|---|
| | *days* | *gm.* | *gm.* | *gm.* | *gm.* | |
| 1 | 20 | 29.4 | 0.150* | 0.74 | 32.4 | 13.5 |
| 2 | 20 | 31.4 | 0.030* | 0.15 | 34.1 | 27.5 |
| 3 | 20 | 30.4 | 0.210* | 1.04 | 31.9 | 16.0 |
| 4 | 20 | 29.0 | 0.267* | 1.39 | 29.5 | 4.5 |
| 5 | 20 | 32.8 | 0.074* | 0.39 | 33.2 | 10.0 |
| 6 | 20 | 29.0 | 0.175† | 3.01 | 28.4 | 2.5 |
| 7 | 20 | 30.5 | 0.088† | 1.50 | 31.7 | 5.5 |
| 8 | 20 | 32.3 | 0.029† | 0.50 | 34.6 | 7.5 |
| 9 | 20 | 31.3 | control | | 35.4 | 45.5 |
| 10 | 20 | 28.4 | control | | 31.3 | 25.0 |

* Residue after removal of lipoid.
† Lipoid extract.

this preparation and the observed toxicity suggested the testing of choline in the form of the choline hydrochloride. This hydrolytic derivative of the lecithins in a 11 mg. dose gave an inhibition of 43 per cent.

## DISTRIBUTION OF THE INHIBITORY AGENT AND ITS LACK OF SPECIFICITY

A limited investigation of the lipoid inhibitor content of the different organs was made. Chloroform extraction of rat heart muscle was followed by extraction with alcohol, and the two fractions tested separately on rat kidney. The former gave an inhibition of 22.6 per cent and the latter 24 per cent. Fresh rat liver dehydrated

* Prepared from Brewer's yeast by Dr. Wm. C. Austin. (See University of Chicago Abstracts of Thesis, Science Series, 2, 337.)

with acetone was given four successive extractions with absolute alcohol for a total of 30 hours and the combined extracts tested on rat kidney. The percentage of inhibition was 29.6 per cent.

A number of determinations of the effect of kidney lipoids upon the proliferative activity of the rat liver were made. To do this an 8 mm. disk of liver for paraffin embedding was cut from the formalin-fixed liver and from this paraffin sections were made for staining in

TABLE II

*Experiment 39*

*Effect of Lipoid Extract of Kidney on the Mitotic Rate of the Liver*

| No. of rat | Age | Weight at injection | Dosage | Dosage equivalent of fresh kidney | Weight at autopsy | Average No. of mitoses | |
|---|---|---|---|---|---|---|---|
| | | | | | | Kidney | Liver |
| | *days* | *gm.* | *gm.* | *gm.* | *gm.* | | |
| 1 | 21 | 43.6 | 0.096* | 3.89 | 42.4 | 14.5 | 17.0 |
| 2 | 21 | 42.1 | 0.024* | 0.97 | 44.0 | 30.5 | 13.0 |
| 3 | 21 | 43.9 | 0.096† | 0.58 | 39.3 | 14.5 | 3.0 |
| 4 | 21 | 40.9 | 0.024† | 0.15 | 41.0 | 10.0 | 6.0 |
| 5 | 21 | 46.1 | control | | 49.2 | 38.5 | 90.0 |
| 6 | 21 | 46.8 | control | | 49.6 | 52.5 | 23.0 |

* Combined ether-alcohol extract. † Residue after removal of lipoids.

hematoxylin and eosin. All mitoses in the hepatic cells were enumerated in several sections. Although there was a wider variation in the mitotic counts made on the livers of the control animals than was noted in the kidneys, conclusive evidence of the inhibitory effect of the kidney lipoids upon liver proliferation was found in the single experiments and in the average for all the experiments. In Table II details of an injected litter are tabulated.

## INHIBITORY ACTIVITY OF THE KIDNEY RESIDUES

When separate extractions permitted it, the various individual lipoid fractions were tested and in all experiments the inhibitory effects of the residues were determined. Regardless of the method of extraction the final residue remained inhibitory. Doubts exist in regard to the cause of this inhibition. In a majority of the experiments the percentage of inhibition shown by sediments was between 50 and 70. These residues, of course, contained bulky insoluble fiber which was present undissolved in the peritoneal cavity

at the time of autopsy. The fiber alone caused an inflammatory reaction and it was not always free from bacteria.[17] The insolubility of parts of extracts "A" and "B," Chart 1, may account for some of the inhibition that was obtained by these suspensions. Intraperitoneal injections of physiological saline solution and of low concentrations of certain other salts do not inhibit. This was well brought out in numerous tests made by us of extracts fractionated by isoelectric precipitation.

## Discussion and Summary

The literature dealing with the effect of lipoids on growth is contradictory. Danilewsky[18] found that tadpoles with lecithin added to the water in which they were kept increased in weight faster than control ones kept in ordinary water, but Goldfarb[19] found no evidence of weight increase brought about by lecithin administration. Robertson[20] in mice fed with lecithin observed a decrease in body weight. Our rats were always weighed at the time of injection and at the time of autopsy but longer observations were not made. At the 24 hour period the increase in weight often was somewhat less than that of the litter-mates (Table I). Our experiments show that the lipoid extracts of the kidney, myocardium and liver exert an immediate antigrowth effect on the kidneys and also on the liver. As shown in Table II, the larger doses almost eliminate mitotic division. The evidence now at hand points to the phospholipids as the inhibiting agent. Previously, one[21] of us found that a trichloracetic acid precipitate of an acid alcohol extract of kidney which was rendered lipoid-free by chloroform extraction inhibited mitotic proliferation of the kidney, but the amount of this substance present in kidneys is very small since the inhibiting dose was equivalent to 20 gm. or more of fresh kidney. In unpublished experiments it was found that this non-lipoid substance could be obtained equally well from the heart muscle and that it also inhibited liver proliferation.

An observation on the removal of the inhibiting agent by changes in the hydrogen ion concentration of aqueous solutions was made many times and may be of significance in explaining the relation between the lipoid and protein fractions of the extracts. When the pH of acid aqueous extracts was brought to 8–8.3 by the addition

of alkali the clear supernatant liquid was no longer inhibitory, and the full inhibiting effect was present in the precipitate. We were of the opinion that the lipoids were thrown out of solution by the isoelectric precipitation of the protein. Sittenfield, Johnson and Jobling,[22] in a study of Rous sarcoma, held the view that the inhibiting agent present in filtrates was "apparently combined with the globulin fraction."

Since a technic such as that used by us focuses attention directly on the karyokinetic changes, our interest in the nuclear division was continuously aroused. In the preceding paragraph the presence in the kidney of a non-lipoid inhibiting agent was mentioned, but the amount in terms of inhibition per gram of fresh kidney is as small as 1/40 of that exerted by the extractable lipoid. Also it is clear that certain of the hormones inhibit proliferation of the cells that produce them. It is enticing to look upon the inhibition produced by excess insulin, thyroxin, or parathyroid extract as a display of automatic self regulation of growth and metabolic activity. But because these substances exert such a profound influence on general metabolism, the view is at present speculative. With the phospholipids forming an integral and necessary part of the various cells it may be presumed that under our experimental conditions they enter the cells from the blood stream, which carries an excess brought about by absorption from the peritoneal cavity of the injected lipoid. The way in which the excess lipoid arrests the initiation of new mitoses in the cells of the renal tubules is not clearly indicated at this time.

From the experiments presented the conclusions are drawn: (1) that the lipoids of organs exert an antigrowth effect on the kidney and liver of young rats into which they are injected; (2) that the inhibiting effect exerted by the lipoids is a potent one, since the quantity contained in 0.5 gm. of fresh kidney is active; (3) that the inhibiting substance is probably in the phospholipid fraction; (4) that it is not specific and is not limited in its action to one or more organs; and (5) that it is widely distributed in the body.

An explanation of the function of lipoids in the regulation of cell growth must await investigation of other factors concerned in nuclear division.

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# CONGENITAL MEGACOLON *

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The object of this paper is to report a case of *megacolon congenitum*, which in its principal pathogenetic features corresponds exactly with Hirschsprung's classical description of the disease. The case is unusual on account of the physical proportions of the patient, the long duration of the symptoms, and the definite mechanical relation of the lesion to the patient's death.

To present a comprehensive review of the vast literature since 1886 in a single report of this nature would be difficult. Briefly, however, one should bear in mind three distinct classifications of the disease etiology which have grown up in the last half century. There are still numerous reports of the clinical histories and autopsy findings each year in support of Hirschsprung's pioneer theory that the intestinal dilatation and hypertrophy are of a prenatal, developmental nature which, in its genuine form, is never found to arise from an obstruction of a tangible type or from a postnatal lesion. Opposed to Hirschsprung's [1] original theory that the persistent constipation which commences shortly after birth is a consequence of congenital dilatation and hypertrophy of the colon is Lehmann's [2] contention that the hypertrophy and dilatation must necessarily follow the chronic constipation. This writer, favoring the second theory that an organic obstruction, whether in the form of anal atresia, valvular closure, tumor or kinking of the distal gut is always present, contends that the hypertrophy is of the nature of a "work-hypertrophy" and cannot antedate the obstructive constipation. Aschoff,[3] too, prefers the concept of "work-hypertrophy" to explain the pathogenesis of the disease. Actually, in the findings of a number of authors, the degree of hypertrophy in the intestinal wall decreases from the sigmoid colon to the ileocecal valve, in striking analogy to the pyloric hypertrophy which decreases in degree from the *canalis egestorius* to the cardia.

* Received for publication September 11, 1934.

In recent years a third viewpoint as to the etiology of megacolon has been brought forward, a viewpoint that is entirely in keeping with the developing trend toward the neurogenic etiology of disease in all departments of medicine. Ogawa [4] suggests a relative insufficiency of the intestinal plexuses with subsequent stasis of fecal material, dilatation, and also secondary hypertrophy of the muscle layers. Cameron [5] has described absence of the cells of Auerbach's plexus. Dott [6] and Adamson and Aird [7] have performed sympathectomies for the successful treatment of megacolon, and the experimental parasympathectomies of the latter authors, with the production of megacolon in cats by affording a preponderant influence of the pelvic sympathetic nervous system, are interesting. These writers feel that an indisputable argument in favor of a neurogenic origin of the disease is the occasional association with it of a dilated urinary bladder, the only feature that bladder and lower colon share in common being their nerve supply. Neugebauer,[8] who also regards the finding of a dilated urinary bladder as of more than incidental importance, seeks an explanation in the development of this organ from the allantois, which in turn originates from the anterior wall of the end gut.

The ingenuity often expressed in neurogenic speculation may be recognized in Knittel's [9] theory of the pathogenesis of megacolon. He associates the disease with a general vasoneurotic condition and regards it as a vegetative dysergia, a diathesis similar to that which is frequently held responsible for gastric ulcer. The microscopic capillary findings here, he holds, are generally strongly positive.

Finney,[10] in his monograph on the subject, enumerates nine different hypotheses suggested by a multitude of workers in their endeavor to explain the etiology of the affection. They are all more or less closely related to the three larger divisions which have been mentioned above.

## Report of Case

*Clinical History:* The clinical history of the case, which came to autopsy on May 30, 1934, was obtained from the Department of Health of Yale College, and from the patient's own physician. From early infancy the patient had been afflicted with a markedly distended abdomen which at all times was in extreme disproportion to his general physique. The usual history of infrequent bowel movements, separated by weeks of constipation and often elicited only by cathartic or enema, is given. Nevertheless, the patient reached a height of 6 feet, was graduated from college, and finally became so accustomed to the

difficulties associated with his condition that he came to regard himself as enjoying relatively good health. The remarkable tolerance of this affection on the part of adults has been demonstrated many times. A young man, with symptoms dating from early childhood, is described by Federn [11] as having served in a soldier's capacity. Another patient was quite able to participate in strenuous sport.[12]

Our patient, at the time of death, was a student of drama and was considered to be of more than average ability. It is said that he appeared to carry himself almost arrogantly, probably because of the expansion of the lower part of the thorax and the lordosis, both of which usually accompany the condition.

The extent of the condition present in October, 1933, 9 months prior to the patient's death, may be construed from the routine roentgenogram of the chest made by the college Department of Health at this time (Fig. 1). The diaphragm, particularly on the left, is eventrated, the heart is displaced to the right and beneath the dense band of shadow which represents the left diaphragm is the gas-filled contour of what is probably a distended loop of the large intestine. At this examination the patient complained only of chronic constipation, was strongly disinclined to follow treatment of any nature and was lost track of during the following months.

On the morning of May 30, 1934, he was discovered in a sitting posture and gasping for breath by a classmate who had seen him perfectly well on the previous evening. He complained that he could not breathe in a prone position and had, therefore, not slept that night. A physician was summoned, but the patient died before his arrival.

## Autopsy Report

The lips, perioral skin, and the nailbeds of all the fingers and toes were tinged a light blue. The abdomen was enormously but symmetrically distended. It not only bulged anteriorly, to the complete obliteration of the umbilical depression, but the flanks and the soft tissues of the lumbar region on both sides of the vertebral column were also ballooned out. The percussion note was alternately tympanic and dull. Numerous old striae marked the tense skin on either side of the midline. The chest was likewise definitely expanded in its lower portion, the intercostal spaces being widened to 4 and 5 cm. The circumference of the body at the umbilical level measured 125 cm. and the greatest abdominal circumference, about 3 cm. above this point, was found to be 135 cm.

The picture which was presented to view with the exposure of the peritoneal cavity and the removal of the chest plate was accurately reproduced by our artist during the autopsy (Fig. 2). It may be seen that the coils of small intestine, which appeared only slightly distended, were found at the extreme left of the abdominal cavity, in a position normally occupied by the descending colon. A greatly

distended portion of large intestine, identified as the ascending colon, held a central position in the cavity and extended high up to the level of the third rib, at which point the first part of the transverse colon was seen to have raised the diaphragm still higher to a level almost parallel with the left clavicle. The transverse colon came down between the small intestine on the left, and the descending colon assumed a position anterior and to the right of the ascending colon. The descending colon, at a point approximately corresponding to its juncture with the sigmoid, had elevated the right dome of the diaphragm to the level of the third rib. The sigmoid, in turn, lay concealed behind the ascending colon. The dilatation included the rectum as well. The glistening serosal surface of the whole large intestine was marked by the broad branchings of the mesenteric veins. There was no trace of haustra, tænia, or appendices epiploicae. The wall of the entire gut from the ileocecal valve to the internal rectal sphincter had a curious leathery feel. This same length of intestine, stretched out after removal from the peritoneal cavity, measured 250 cm. Some idea of the degree of dilatation may be had from the dimensions which were taken *in situ*. The ascending portion of the colon had a circumference of 35 cm. The circumference of the descending portion was even greater, measuring 56 cm.

One of the largest megacolons reported in the literature, from Formad's [13] 23 year old patient who was termed a "balloon-man" during life, and compared with an "ox-gut" at autopsy, reached a circumference of 33 to 44 cm. Several examples of megacolon, which appear, however, to have involved little more than the sigmoid and in no instance have included the entire large intestine, have shown even greater dimensions. Vulpian [14] found the circumference of the most enormous sigmoid dilatation to be 70 cm. Figures of 67 cm. and 55 cm. were found by Walker and Griffiths,[15] Banks,[16] and Hoffmann.[17] In these cases the relatively rare example of a colon dilated in all its parts was not present, and hence the 10 liter capacity of the colon in Hoffmann's case is not striking.

After enormous quantities of pasty, foul-smelling, gray-brown fecal material had been removed from our specimen the lumen was filled for the purpose of fixation with 30 liters of 10 per cent formalin. To rule out any possible increase in capacity produced by stretching during this procedure, a series of readings of the circumference

of the gut prior to its removal were taken. These, when calculated with the known length of 250 cm., yielded a result that corresponded closely to the established 30 liters. Several days later the specimen was sectioned and its mucosal surface examined for ulceration or any form of mechanical obstruction. None was seen. The transverse folds appeared ironed out, velvety and entirely intact. A notable difference in degree of hypertrophy, with gradual decrease from the rectum to the ileocecal valve, was manifest grossly in the intestinal wall. Microscopic preparations showed the hypertrophy to involve the muscular coats, including the muscularis mucosae, with a particularly striking increase in breadth of the circular layer. No increase in the fibrous connective tissue between the muscle fibers, as seen by Concetti,[18] could be determined. There was some small round cell infiltration of the submucosa. No abnormalities of number or structure of Auerbach's plexuses were noted.

From the photograph of the black and white drawing (Fig. 2) it may be seen that with the bulk of the liver rotated posteriorly, the anterior aspect of this organ lay parallel with and was compressed against the right diaphragm, permitting only the inferior margin and a small portion of the posterior aspect, including the gallbladder, to anterior view. The inferior margin of the right lobe of the liver was thin, elongated and concave on its posterior surface, evidently the consequence of chronic intestinal pressure from below. Both lungs were similarly affected topographically. They likewise had been rotated posteriorly. The lower margin of the right lung was at a level with the third rib. Only a small portion of the inferior margin of the left lung was visible, and this protruded slightly below the left clavicle. With the exception, however, of a deep purple and dense area of atelectasis on the upper lateral aspect of the right lower lobe, which measured but a few cm. in diameter, the pulmonary parenchyma was quite crepitant. The elevation of the heart to the upper mediastinum, and its marked displacement to the right were striking. The acute cardiac compression, which produced a kind of tamponade to the normal ventricular dilatation and contraction, together with the extreme passive congestion of the viscera, especially marked in the microscopic preparations of the liver, give us a picture of the mechanism of death which overtook our patient.

## Discussion

The manner of the patient's death, reconstructed from the autopsy findings, as well as from the brief account of his extreme respiratory distress during his last few moments of life, is perhaps most worthy of our consideration.

From a table of 17 cases selected by Concetti,[18] in which the cause of death was definitely known, 10 were recorded as resulting from acute colitis. Marked cachexia and perforation of the intestine complicated 2 of these. Of the remaining 7 cases, death resulted in 4 from cachexia alone, 2 were postoperative and 1 resulted from pneumonia. The colitis in the majority of the cases cited was accompanied, as established at autopsy, by a widespread ulceration of the dilated portion of the gut. Finney,[10] who in 1908 had reviewed all the literature on the subject up to that time, stated that heart failure, as well as peritonitis, the result of perforation and diseases of the respiratory organs, particularly bronchitis and bronchopheumonia, were the most common of the intercurrent affections leading to death.

The clinician is frequently faced with significant compression phenomena, such as in our own case. The abdominal distention compresses the thoracic organs and the posterolateral margins of the lungs become atelectatic.[11,19] The diaphragm in many cases is lost to the respiratory mechanism; breathing becomes thoracic in type and very difficult. Auxiliary respiration with deep retraction at the jugulum and occasionally of the lower intercostal spaces have been observed.[20] Barth[21] described a patient in whom the pulmonary percussion note reached only to the second rib on the left and to the fourth rib on the right. In the same patient the apical impulse was felt in the second interspace. In a 60 year old man, 1 of the 5 cases reported by Wilkie,[22] the upward displacement of the liver and the abnormal height of the cardiac dullness were established clinically. Among the symptoms several acute attacks of respiratory distress were noted. This patient made a complete recovery following a preliminary colostomy and subsequent resection of the dilated portion of the bowel.

Definite impairment of cardiac function has been recorded. Perthes[23] noted a periodic bradycardia which disappeared promptly upon the elimination of large quantities of fecal material. Other

authors have found the pulse rapid and feeble.[24] It is believed that the cardiac weakness is not only a result of compression of the heart and lungs,[25] but that it is also due to the chronic resorption of the products of intestinal putrefaction.[17] The pathologist has been able to find practically negligible evidence of the latter.

## Summary

In this report of a *megacolon congenitum* in a 22 year old male stress has been laid upon the magnitude of the intestinal dilatation and its almost exclusive rôle in precipitating the death of the patient. The mechanism of death has been considered in some detail and has been ascribed to cardiac and pulmonary compression, which resulted in the clinical phenomena of acute congestion, strikingly present also at autopsy.

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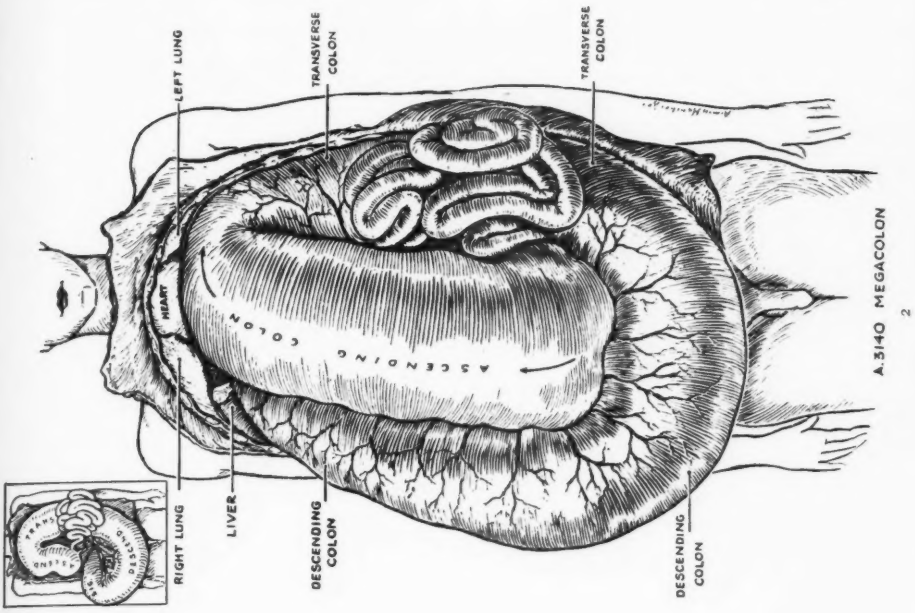
## DESCRIPTION OF PLATE

### PLATE 55

FIG. 1. Photograph of roentgenogram of chest showing eventration of left dome of diaphragm, caused by enormously distended loop of large intestine.

FIG. 2. Photograph of black and white drawing of megacolon at autopsy, showing the magnitude of the colonic distention with the upward displacement of liver and thoracic viscera.



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Opper Congenital Megacolon